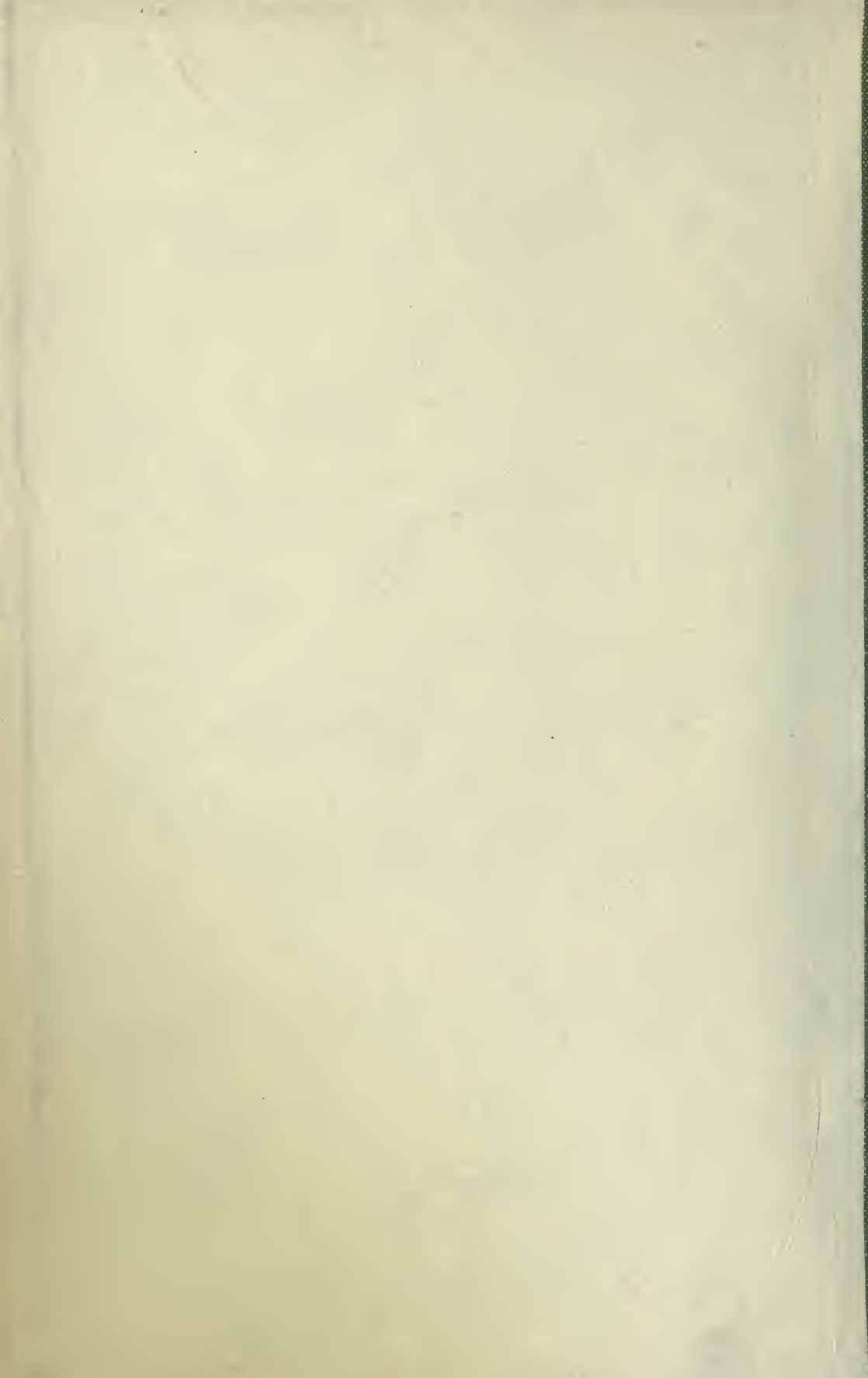



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SOME CHEMICAL BLOOD OBSERVATIONS IN UROLOGIC CASES¹

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The advances which have been made during the past five years in our knowledge of the non-protein blood constituents, have already been found of great value by the internist in the diagnosis and treatment of both nephritis and diabetes. The general surgeon not infrequently finds it necessary to operate upon patients while suffering from these conditions and such diagnostic and prognostic information as the blood tests afford, is of the greatest service in giving him an insight into the surgical risk of an operation. To the urological surgeon who may be called upon to perform a prostatectomy, nephrectomy or nephrotomy, make a decapsulation, etc., the prognostic information which the blood urea or creatinine will give regarding the functional activity of the kidneys, would seem quite indispensable at the present time.

Before entering into a discussion of this question, it may be of interest to recount the more salient facts which have been ascertained regarding the changes which occur in the blood as the result of impaired kidney activity, particularly in comparison with the results of the slightly less recent phthalein test. This latter test, introduced by Rowntree and Geraghty (1) in 1910, not only supplied us with a most valuable diagnostic and prognostic test, but furnished the impetus in this country to numerous investigations on the functional activity of the kidney. With the introduction, three years later, of simple methods of blood analysis, especially at the hands of Folin and his co-workers, the

¹ This paper was read before the Section on Genito-Urinary Surgery of the New York Academy of Medicine on December 19, 1917.

possibilities of these new methods as practical diagnostic tests were quickly appreciated. The literature dealing with the functional kidney tests, including the chemical blood tests, has been so frequently discussed during the past few years that a review of the literature hardly appears appropriate at the present time.

It may be well at the outset, however, to outline the general scheme which we have followed in the chemical examination of the blood. The tests employed cover the ability of the kidneys to eliminate the nitrogenous waste products and the possibilities of hyperglycemia and acidosis. This would appear to be a sufficiently comprehensive scheme to answer the questions which usually arise in the types of cases considered. No doubt it may be possible to arrive at similar conclusions with other modes of attack, but the present method has been found satisfactory.

In cases where it is desired to ascertain the ability of the kidneys to excrete the nitrogenous waste products, determinations are made of the urea, creatinine and in some cases of the uric acid. The normal blood content of these three end products of nitrogenous metabolism may be given as 12 to 15 mgm. of urea nitrogen, 1 to 2 mgm. of creatinine and 2 to 3 mgm. of uric acid, all calculated per 100 cc. of blood (2). There would appear to be little doubt that the very early cases of interstitial nephritis are accompanied by an appreciable rise in the blood uric acid, although a rise in the blood urea can probably be taken as a safer sign of impaired kidney function. It is certainly true that the urea nitrogen falls within very narrow limits for perfectly normal individuals. As soon as one passes to hospital patients, however, figures above 15 are found. Figures over 20 on the usual restricted protein diet of the hospital would suggest impaired kidney function. Creatinine appears to be more readily eliminated than either uric acid or urea, and it is not, as a rule, until the blood urea has doubled, or more than doubled the normal, that there is a very appreciable increase in this purely endogenous waste product derived apparently from muscular metabolism. As pointed out above, the normal for the creatinine of the blood is approximately 1 to 2 mgm. per 100 cc. and a figure as high as 3.5 mgm. can be viewed with very grave concern,

while figures over 5 mgm. are almost invariably indicative of an early fatal termination (3). Obviously cases of this kind, i.e., with over 3.5 mgm. creatinine per 100 cc. of blood, are very poor surgical risks. The only possible exceptions might be cases where the retention was due to some acute renal condition.

In comparing the creatinine and urea of the blood in cases which already give some evidence of renal insufficiency, it may be noted that the creatinine, being almost exclusively of endogenous origin, is less influenced by the intake of protein than urea and constitutes a most satisfactory criterion as to the deficiency of the kidneys, while urea, being largely exogenous in origin, is more readily influenced by dietary changes and constitutes a most sensitive index of the response to treatment.

Some workers have endeavored to obtain more definite information than the blood alone will give regarding the ability of the kidneys to excrete urea, by comparing the urinary excretion with the concentration in the blood. Attention has been given to this particularly by Ambard (4) and McLean (5) who have worked out formulae to express this relationship. Our own experience with this method has been disappointing in that the results have failed to reveal any added information not given by the blood alone (6). We have long felt what Folin (7) has recently stated, viz.,

The complicated mathematical formulas introduced in connection with the Ambard coefficient do not tend to increase one's confidence in that coefficient. It is difficult to see how square roots and cube roots can help to elucidate such a simple metabolism proposition.

The inability to properly excrete the waste products of nitrogenous metabolism is only one of the difficulties which arise as the result of renal disease. As is well known, in chronic parenchymatous nephritis, or nephrosis, the edema is probably dependent, in part at least, on the lowered permeability of the kidneys for chlorides with their consequent retention. It is natural therefore to expect that the excretion of other salts should be deficient, although we have only recently come to appreciate the effect of the retention of phosphates (8). Normally acid

phosphate provides one of the most important mechanisms of eliminating acid. When the phosphate excretion is impaired; bringing about an increase in the (acid) phosphate of the blood (and tissues), an acidosis results. This retention of acid phosphate reduces the ability of the blood to take up and carry away carbon dioxide, or in other words lowers its CO_2 combining power. With the simple apparatus recently devised by Van Slyke the determination of the CO_2 combining power of the blood is very simple and would seem to provide the most satisfactory method of any we possess for ascertaining the degree of acidosis. Because of the well known influence of anesthetics, such as chloroform and ether upon acidosis, the CO_2 combining power of the blood constitutes a very valuable pre-operative test in certain cases.

It has frequently been noted that patients suffering from renal disease show blood sugars which are above the normal limits. A satisfactory explanation for this slight hyperglycemia has only recently been offered (9). The blood of such cases exhibits a correspondingly high diastatic activity, and since it has long been recognized that the diastase excretion of these cases is lowered, this would serve to explain the increased diastatic activity of the blood and in turn of the increased blood sugar.

The importance of the chemical examination of the blood in diabetes is coming to be appreciated more and more. The excretion of sugar by the kidneys is simply one of the body's many factors of safety. The condition to which attention should be directed is the hyperglycemia, and as the disease advances the glycosuria becomes less and less a safe criterion of this, since the permeability of the kidneys for sugar appears to be gradually lowered. Normally the blood sugar varies from 0.09 to 0.12 per cent and in early cases of diabetes one may note an excretion of sugar when the sugar of the blood rises above 0.16 or 0.17 per cent, but in advanced cases blood sugar figures of 0.2 to 0.3 per cent (and even 0.46 per cent) may be noted without the appearance of any sugar in the urine (10). The diastatic activity of the blood, noted above in connection with the hyperglycemia of nephritis, is found to be proportional to the blood sugar in

untreated cases, and would appear to be the blood sugar determinant. No explanation has as yet been found, however, for the rise in the diastatic activity of the blood.

The possibility of a patient being thrown into an acidosis coma as the result of operative anesthesia is much more important in diabetes than in nephritis. The value of a pre-operative determination of the CO_2 combining power of the blood has already been pointed out in the case of nephritis. Practical experience has shown that diabetic patients with low CO_2 combining power rarely survive operative procedures requiring a general anesthetic.

As a control test of another type the phenolsulphonephthalein test has been employed in many of the cases. When proper precautions are taken to secure an accurate collection of urine (catheter), our observations abundantly confirm the reliability of this test. They have also demonstrated the necessity of these precautions, however, and it is partially on this account that we believe greater dependence can be placed on the results of blood analyses.

Obviously when it is desired to ascertain the activity of the kidneys individually, blood analyses are of little value, except in so far as they may indicate that both kidneys are involved or not and thus aid in determining the operative risk. To determine the comparative functional ability of the two kidneys, it would appear necessary to resort to catheterization of the ureters. The output of phenolsulphonephthalein or indigo-carmin after the administration of these drugs or the excretion of urea may be compared. Krotoszymer and Stevens (11) are strong advocates of the phlorhizin test for this purpose.

METHODS OF BLOOD ANALYSIS

It has been our custom, whenever possible, to secure the blood specimens after a twelve to fifteen hour fast, i.e., in the morning before breakfast. It is believed that in this way the possible influence of dietary factors is reduced to a minimum. About 20 to 25 cc. of blood are drawn into a bottle containing

the dried residue of 6 to 8 drops of 20 per cent potassium oxalate to prevent clotting. The various blood analyses were carried out as follows:²

Urea. By a modified Marshall-Van Slyke method, essentially as described by Myers and Fine (2). The enzyme used is that derived from the jack bean. The Nessler's solution employed at present is from a very satisfactory formula furnished us by Drs. Benedict and Bock, which contains 100 grams of mercuric iodide, 70 grams of potassium iodide and 200 grams of sodium hydroxide per liter of solution.

Creatinine. By a modified Folin technique carried out as previously described (2).

Uric acid. By a modification of the Folin and Denis-Benedict method as already described (2).

Sugar. By the method of Lewis and Benedict as modified by Myers and Bailey (10).

CO₂ combining power. By the method of Van Slyke and Cullen (12).

DISCUSSION OF CASES

Observations are reported on 75 cases divided as follows: 58 cases with prostatic obstruction, 7 nephrectomy cases, one double decapsulation in a case of bichloride poisoning and 9 miscellaneous urologic cases. Data have been collected on these cases for the past three years. Although the present series of cases includes only those in which it was found possible or desirable to make blood analyses, none of the cases in which such examinations were made has been deleted from the series reported for any reason whatsoever. Most of these cases were on the surgical service of one of us (J. B. S.), but a few other cases have been included through the courtesy of colleagues. To one of these, Dr. Clarence G. Bandler, we are further indebted for aid in the preparation of the records of these cases.

² In conducting the colorimetric analyses the Duboscq and Hellige colorimeters have been employed, generally the former. It is perhaps worthy of note that recent experience with the American made (Kober) colorimeter of the Klett Co. has shown this instrument to be even superior in some respects to the Duboscq.

In a paper (13) which was read by one of us (J. B. S.) on the post-operative and convalescent period of prostatectomy more than a year ago, attention was called to the value of chemical blood determinations in preventing post-operative complications. Up to the present, however, the observations on the individual cases have not been reported.

The data on the cases of prostatic obstruction are recorded in table 1. From an inspection of this table it is apparent that individuals with prostatic obstruction exhibit higher figures for the urea nitrogen of the blood than the average run of hospital cases. It will be observed, however, that in the first group of operative cases with recovery (cases 1 to 39), the majority of the urea nitrogen figures are below 20 mgm. per 100 cc. of blood, which stands quite in contrast with the fatal cases in the last group (cases 55 to 58). In several instances in the first group of cases (1, 3, 11 and 15), it will be noted that the urea nitrogen figures are close to 30 mgm. per 100 cc. of blood. As indicated by the date of the operation in these cases, they were not operated upon until after preliminary treatment, intended to relieve the nitrogen retention, had been carried out for some time. Unfortunately, with the exception of case 3, we have no observations in this group of cases showing the improvement in the blood picture as a result of the preliminary treatment. As will be noted in the table, the urea estimation in case 30 was not made until a week after the operation and then, apparently, because the patient was not doing well.

The second group contains five cases in which no operation for the relief of the prostatic obstruction was performed. In the first two of these cases (40 and 41), the blood analyses indicated a perfectly good risk, but here operation was not deemed expedient on account of hernia. In the remaining three cases operation was contra-indicated by the blood analyses and also by the clinical symptoms. All three cases died. In case 42 the preliminary treatment was without influence on the blood picture. Case 43 suffered also from diabetes, as shown by the blood sugar. Judging from the CO_2 -combining power of the blood, the acidosis was not marked, still the patient died in coma four

TABLE 1
Chemical blood examinations in cases with prostatic obstruction

CASE	AGE	DATE OF AD- MISSION	DATE OF DIS- CHARGE	DATE OF OPERA- TION	ANESTHETIC	DATE OF BLOOD EXAMI- NATION	BLOOD ANALYSES					PHTHAL- EIN, 200 HOUR	OUTCOME, REMARKS
							Urea N	Creat- inine	Uric acid	Sugar	CO ₂ com- bining power		
							<i>mgm. to 100 cc.</i>	<i>mgm. to 100 cc.</i>	<i>mgm. to 100 cc.</i>	<i>per cent</i>	<i>cc. per 100 cc.</i>	<i>per cent</i>	
1. J. C.....	78	1915 9/7	1915 10/20	1915 9/22	E	1915 9/10	36	2.1	6.0	0.100		50	Alkaline cystitis, cleared up after operation, recovery Still had to be catheterized, improved
2. H. J.*.....	60	9/20	11/16	9/24	E	9/22	18	2.5	7.2	0.090			
3. W. B.....	61	12/7	2/27	12/23	G-O	{ 12/8 12/11 12/17	23 46 22	2.5 2.8 2.4		0.141 0.135 0.159		35 41	Recovery
4. M. N.....	60	2/7	2/28	2/8	G-O	1916 2/8	18	3.3	2.5	0.150			Recovery
5. I. L.....	65	2/8	3/9	2/9	G-E	2/9	13	2.3	2.9	0.141			Carcinoma of prostate, re- covery
6. S. C.....	52	3/8	3/30	3/10	G-E	3/9	12	2.2		0.130			Recovery
7. P. H.....	64	4/17	6/29	{ 4/24 6/10	{ G-O G-E	4/21	14	2.4	7.0	0.120			Both suprapubic and perineal operation, 2nd to remove fibrous ring, recovery
8. M. R.....	54	5/2	6/6	5/4	G-O	5/3	14	1.3	6.7	0.124		49	Recovery
9. J. D.*.....	57	5/18	7/14	5/24	G-E	5/19	15	3.1	5.3	0.110		38	Recovery
10. H. B.....	67	5/22	6/10	5/24	G-O-E	5/23	16	1.3	5.1	0.135		45	Fibrous prostate, recovery
11. H. S.....	68	5/25	7/6	6/1	G-O-E	5/31	29	2.7	7.2	0.264			Cystotomy on 5/25 under local anesthesia, recovery
12. T. B.....	69	6/11	7/11	6/15	G-E	6/13	12	1.9	2.4	0.120		26	Perineal operation, recovery
13. L. P.....	61	7/9	8/20	7/10	G-O-E	7/10	13	1.8	4.9	0.132			Recovery

14. H. D.	73	8/31	10/5	9/2	G-E	9/1	17	2.9	4.0	0.120		Constriction of neck of bladder, adenoma of prostate, perineal operation, recovery
15. G. M.	73	9/4	11/7	9/11	G-O-E	9/6	28	2.0	3.5	0.165		Perineal operation, recovery
16. S. A.	65	9/7	11/1	9/10	G-E	9/9	20	1.9	0.210		45	Recovery
17. J. B.	52	10/23	11/24	10/25	G-E	10/24	24	2.3	0.111			Also removal of vesical calculi, recovery
18. O. K.	66	11/4	12/30	11/10	G-O-E	11/10	18	2.6	5.7	0.336		Slight glycosuria, recovery
19. C. M. *	53	11/20	12/10	11/23	G-E	11/21	13	2.4	4.7	0.123	34	Recovery
		1917	1917	1917		1917						
20. J. L.	66	1/2	2/2	1/5	G-O	1/3	16	1.8	5.0	0.132		Recovery
21. C. E. *	76	1/26	2/27	1/30	G-E	1/27	17	2.8	6.1	0.123	39	Recovery
22. M. S.		1/29	2/24	1/31	G-O	1/30	14	2.1		0.117		Recovery
23. M. B.	67	1/30	4/5	2/1	G-O	2/1	11	1.7		0.123	62	Recovery
24. G. S.	67	2/9	3/9	2/13	G-O	2/10	9	1.3	9.5			Recovery
25. C. B.	60	2/15	4/15	2/17	G-E	2/16	21	2.6	5.0	0.120		Tuberculosis of prostate; clinical diagnosis, carcinoma, perineal prostatectomy; improved
26. L. W.	81	2/18	3/22	2/24	G-O-E	2/20	21	2.5	5.5	0.124	41	Fibrous prostate, perineal operation, recovery. Positive Wassermann
27. H. R.	55	2/19	3/30	2/21	G-E	2/20	20	2.4		0.108	57	Improved (left hospital at own risk)
28. C. J.	63	2/19	4/5	2/28	G-O	2/21	16	2.4		0.136	36	Recovery
29. D. M.	53	2/21	3/23	2/28	G-O	2/27	18	2.2		0.114		Recovery
30. S. C. *	76	3/4	4/16	{ 3/5 3/21	{ G-O-E G-O	3/13	59	3.2	3.1	0.200	51	2nd operation to close wound, wound not completely healed, syphilitic, improved. Note blood analysis one week after first operation

TABLE 1—Continued

CASE	AGE	DATE OF AD- MISSION	DATE OF DIS- CHARGE	DATE OF OPERA- TION	ANESTHETIC†	DATE OF BLOOD EXAMI- NATION	BLOOD ANALYSES					PHTHALIC ACID TWO HOUR OUTPUT	OUTCOME, REMARKS
							Urea N	Creat- inine	Uric acid	Sugar	CO ₂ com- bining power		
							mgm. to 100 cc.	to mgm. 100 cc.	to 100 cc.	per cent	cc. per 100 cc.	per cent	
31. J. D.	60	1917 3/26	1917 5/1	1917 4/7	G-O	1917 3/27	18	3.4		0.150			Also removal of vesical cal- culus, recovery
32. H. S.	70	4/9	5/10	4/13	G-O	4/10	25	2.9	4.2	0.111			Recovery (6 min. operation).
33. H. K.	52	4/24	5/21	4/28	G-O-E	4/24	17	2.8		0.117		31	Contracted neck of bladder, fibrous prostate, recovery
34. M. M.	73	7/2	8/6	7/3	G-O	7/3	24	2.5	6.7	0.105			Recovery
35. B. W.	65	7/21	8/18	7/25	G-E	7/24	25	2.8		0.137			Recovery
36. S. H.	52	7/30	10/6	9/3	G-O	8/31	22	2.4	6.4	0.135			Recovery
37. W. S.	71	9/10	10/3	9/13	G-O	9/11	21	2.2		0.126			Recovery
						11/21				0.328	45		On admission urine contained
						11/24	29	1.5	3.3	0.184	46		6.2 per cent of sugar, small
						11/26				0.165	53		amount of albumin and
						11/30	22			0.210	58		trace of acetone. At once
						12/14	20	2.8		0.336	5		placed on restricted diet.
													Urine sugar free 1/26. Re- covery
38. S. F.	61	11/20	1/18	11/21	G-O	11/24	29	1.5	3.3	0.184	46		Complete recovery from pros- tate operation but died
						11/26				0.165	53		after resection of sigmoid
						12/14	20	2.8		0.336	5		for adeno-carcinoma on 12/7
39. H. D.	73	10/18	12/13	10/21	G-O	10/21	22	1.9	6.1	0.120			under G-O-E

40. J. M.	70	3/ 1	3/ 3		3/ 3	14	2.1	3.3	0.135	21	Observation only, only moderately enlarged prostate, left scrotal hernia
41. M. M.	60	5/19	6/11		{ 5/25 6/ 1	12	1.9		0.108		Observation only, hernia, also refused operation
42. H. S.	66	8/29	9/ 9		{ 8/31 9/ 7	24	2.5		0.174	0	Chronic nephritis, poor operative risk, no operation, died in uremia
43. M. V. *	64	6/ 2	6/10		6/ 6	33	3.3		0.30	52	Suprapubic cystostomy only 6/9 under local anesthetic, died in diabetic coma
44. J. S.	69	5/ 3	5/19		{ 5/ 4 5/15	89 104	9.4 7.5	1.6	0.165 0.201		Cystostomy and drainage of bladder only on 5/5 under G-E-C, very poor risk, died
45. J. G.	73	2/23	3/ 5	2/26	{ 2/25 3/ 3	14	2.9	4.8	0.117	46	Died from lobar pneumonia
46. J. J.	55	2/29	3/21	3/ 1	3/ 1	33	2.7	5.0	0.147		Also removal of vesical calculus, died from lobar pneumonia
47. H. L.	64	11/ 9	12/30	11/18	{ 11/14 11/22	21	3.5	6.0	0.135		Died, bronchial pneumonia
48. J. H.	71	3/ 1	3/26	3/24	3/22	19	2.4	6.9	0.135	66	Myocarditis, 0.5 per cent sugar in urine, died lobar pneumonia
49. M. G.	43	4/ 9	4/16	4/11	4/10	13	2.1	2.5	0.111		Died from secondary hemorrhage, five days after operation
50. M. S.	60	4/13	4/20	4/18	4/18	15	3.5		0.126		Died from gastric dilatation
51. N. B.	72	5/13	5/20	5/15	5/14	18	2.1	3.1	0.123		Died—circulatory failure, five days after operation

TABLE 1—Concluded

BASE	AGE	DATE OF AD- MISSION	DATE OF DIS- CHARGE	DATE OF OP- ERA- TION	ANESTHETIC†	DATE OF BLOOD EXAM- INATION	BLOOD ANALYSES				PHTHAL- EIN TWO HOUR OUTPUT	OUTCOME, REMARKS
							Urea N	Creat- inine	Uric acid	Sugar	CO ₂ com- bining power	
							mgm. to 100 cc.	mgm. to 100 cc.	mgm. to 100 cc.	per cent	cc. per 100 cc.	per cent
52. A. H.	64	9/14	9/27	9/19	G-O	9/18	17	2.3	2.8	0.117		Died from secondary hemor- rhage, eight days after op- eration
53. T. K.	79	1/14	2/28	1/18	G-E-C	{ 1/18 2/18 2/25 }	20 41 45	1.3 3.7 2.6	2.0 6.0		46 37	Wound had been healed for sometime, died from chronic parenchymatous nephritis five weeks after operation
54. T. K.	62	3/ 3	6/26	3/ 8	G-O	{ 2/25 3/ 3 }	53 48	4.9 3.0	4.9 7.1	0.132 0.132		Wound healed 1 month be- fore death, died from lobar pneumonia
55. E. W.	69	2/ 5	2/20	2/12	Novo- caine	{ 2/ 8 2/ 9 2/15 }	45 44 104	4.9 4.2 6.7	2.6 3.8 9.1	0.132 0.117 0.165	34	Wassermann positive. Self retaining catheter used, blood indicated a very poor risk, died
56. J. C.	65	6/20	7/ 6	7/ 5	G-O	{ 6/20 6/27 12/22 }	38 29 30	3.9 2.6 2.7	7.2 7.4 6.9	0.132 0.204 0.164		Uremic symptoms, poor risk, died.
57. W. McD...	64	12/19	12/30	12/22	G-O	12/22	30	2.7	6.9	0.164		Died
58. E. P.	74	8/31	9/ 9	9/ 5	G-E	9/31	37	2.3	7.6	0.144		Died

* Patients on service of colleagues. † G = gas, O = oxygen, E = ether and C = chloroform.

days later. Case 44 shows the typical blood picture of terminal chronic interstitial nephritis. Cystotomy was performed here simply with the idea of giving the patient temporary relief.

In the third group (cases 40 to 54), one case died from gastric dilatation, five cases died from pneumonia, two from hemorrhage, one from parenchymatous nephritis, and one from circulatory failure. The blood analyses indicated the first nine of these ten cases to be good operative risks. The high figure for urea nitrogen found in the second blood analysis of case 45 was obtained two days preceding the death from pneumonia. Case 53 developed chronic parenchymatous nephritis sometime after operation and at the time of death, about five weeks later, showed considerable retention of urea and quite marked acidosis (CO_2 -combining power of 37). The blood creatinine was not especially affected, a finding quite in harmony with the observations we have made in other cases of parenchymatous nephritis. Judging from both the urea and creatinine findings, case 54 was a poor risk at the outset. A week of preliminary treatment produced little change in the urea (a drop from 53 to 48), although the drop in the creatinine was more marked. The fact that the patient had continued to remain in the hospital is significant of his condition.

In the fourth group, the outcome of the four fatal cases was in complete accord with the results of the blood analyses. In the light of the chemical blood analyses, all four cases were obviously poor surgical risks. Case 55 was originally a ward case of one of us (J. B. S.). On account of the blood findings, an operation was regarded as contra-indicated. At the request of one of our colleagues, the case was turned over to him and the operation performed under spinal anesthetic, owing to the low CO_2 -combining power of the blood and the high urea. It is interesting to note that the patient died a week later with a blood picture typical of chronic interstitial nephritis. Case 56 showed some improvement as a result of the preliminary treatment, the urea nitrogen of the blood dropping from 38 to 29 mgm. following the first week's treatment. After another week of treatment, a prostatectomy was performed under gas and oxygen anesthesia. The

patient died on the following day. The result with the two remaining cases was similar. Judging from these four cases, urea nitrogen figures of 30 mgm. or over are a very bad pre-operative sign in prostate obstruction.

An interesting observation of problematic influence upon the cause of death, is that all the cases of this group who had chloroform anaesthesia died.

Chemical blood observations on seven nephrectomy cases are recorded in table 2. These data appear to present less of interest than the prostate cases. All cases in this series recovered except the last. Four of the six cases with recovery show quite normal figures for urea nitrogen, but in cases 1 and 3 the figures are rather high, 33 and 29. It is of interest to note that the phthaleins in these cases were 31 and 33 respectively, in perfect harmony with the blood findings. Why the activity of the kidneys, as a whole, should have been affected more in these two cases than the other four is difficult to explain, although the infective nature of the condition may have been the cause in the first case. The blood findings in the last case are of interest only in so far as they illustrate the blood picture just before death from nephritis. Unfortunately, no blood analyses were made in this case until nine days after operation.

Table 3 presents data on nine miscellaneous cases, seven of which came to operation. The last two cases were not operated upon, in part, because of the advanced renal disease which existed, as shown by the blood analyses. It is of interest to note in comparison with case 1 of the preceding table, that case 1 in this series, with a septic kidney, likewise showed a high urea nitrogen (28 mgm.). Comparatively normal figures were found in the next five cases. The low phthaleins in cases 4 and 5 only admit of partial explanation. In case 4 the excretion of urine during the test was poor, while in case 5, although the output of urine was excellent, there appeared to be a delay in the excretion of the dye. Case 5 was a diabetic with a blood sugar of 0.39 per cent, but it is interesting to note that a CO_2 -combining power of 60 indicated an absence of acidosis. Case 7 appears to be quite an unusual one. This patient, a physician, with a

TABLE 2
Chemical blood examinations in nephrectomy cases

CASE	AGE	DATE OF AD- MISSION	DATE OF DIS- CHARGE	DATE OF OPERA- TION	ANES- THETIC	OPERATION, REMARKS	DATE OF BLOOD EXAMI- NATION	BLOOD ANALYSES				PHRE- NIN 2 HOUR OUTPUT
								Urea N	Creat- inine	Uric acid	Sugar	
								mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	per cent	per cent
1. J. A.*.....	29	2/24	3/26	2/26	G-E	Stone in right kidney with multiple septic infarcts, nephrectomy, acute infective nephritis, re- covery	2/29	33	2.9	4.7	0.18	31
2. A. L.....	38	5/15	6/5	5/17	G-E	Pyonephrosis of right kidney, neph- rectomy, recovery	5/17	18	1.7	5.8	0.136	
3. M. Y.....	64	11/17	12/24	12/4	G-E	Hypernephroma, right, nephrec- tomy, recovery	11/21	29	1.5		0.144	33
4. J. C.....	41	12/4	1/1	12/7	G-E	Tuberculous pyonephrosis, left kid- ney, nephrectomy, recovery	12/5	15	1.4		0.117	
5. R. F.*.....	28	8/25	9/28	9/12	G-E	Left hydronephrosis, nephrectomy, recovery	9/7	17	3.3		0.105	50
6. V. P.*.....	32	9/7	9/28	9/14	G-E	Right tuberculous kidney, nephrec- tomy, recovery	9/11	13	2.2		0.117	65
7. A. F.....	45	2/7	2/19	2/9	G-E	Multiple calculi of left kidney, nephrectomy, calculus of right kidney, nephrotomy. Pathologi- cal report: chronic pyeloneph- ritis and lithiasis. Died	2/18	114	6.1	12.4	0.225	9

* Cases on service of colleagues.

TABLE 3
Chemical blood examinations in miscellaneous urologic cases

CASE	AGE	DATE OF AD-MISSION	DATE OF DISCHARGE	DATE OF OPERATION	ANESTHETIC	OPERATION, REMARKS	DATE OF BLOOD EXAMINATION	BLOOD ANALYSES				PTHAL-LEIN 2 HOUR OUTPUT
								Urea N	Creatinine	Uric acid	Sugar	
								mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	per cent	per cent
1. W. B.....	36	1915 10/29	12/7	11/3	G-E	Horse shoe kidney and multiple septic infarcts, nephrotomy, recovery	11/12	28	2.6	1.9	0.15	
2. F. M.....	50	1916 3/5	3/18	3/8	G-E	Carcinoma of bladder, resection, transplantation of right ureter, died from cardiac failure	3/6	19	3.0	4.8	0.138	52
3. A. M.....	27	3/29	4/18	4/1	G-E	Renal calculus, nephrotomy, recovery	3/31	19	4.2	4.8	0.147	
4. J. H.*	69	1/25	2/14	1/29	G-E	Vesical calculus, suprapubic cystotomy, recovery	1/26	18	1.9		0.184	13†
5. W. G.....	64	6/6	7/18	6/12	G-E	Tumor of bladder, partial resection, recovery. Mild glycosuria	6/6	15	2.3	5.0	0.39	18
6. C. M.....	60	5/29	6/8	6/5	G-E	Carcinoma of bladder, exploratory cystotomy, inoperable carcinoma, died (cardiac)	6/1	15	2.2		0.123	
7. H. B.....	40	1/22	2/14	1/24	G-E	Polycystic kidney, nephrotomy, improved. Still improved at end of 6 months†	1/23	75	8.3	4.5	0.192	
8. S. W.....	56	1/5	1/16			Bacteremia, suppression of urine, lobar pneumonia, no operation, died	1/7 1/14	14 224	1.3 9.1	2.8 12.5	0.108 0.126	4.4§
9. J. W.....	57	5/6	5/18			Carcinoma of bladder, operation contra-indicated, died in coma	5/15	95	8.2		0.159	

* Patient on service of colleague.

† Elimination of urine small.

§ Obtained on 1/10.

‡ Six weeks after incising the cysts of one kidney, the patient was again engaged in active practice, which was continued for just a year. Following overwork, and exposure during a snow storm the latter part of February, the patient developed severe pains in the opposite side. After urgent request the cysts in this kidney were incised, but the patient lived only a few hours, and died on the day the proof of this paper was received. Unfortunately we were unable to obtain another specimen of blood.

polycystic kidney, a urea nitrogen of 75 and a creatinine of 8.3 mgm., showed considerable improvement after the cysts were incised and is still improved, nearly a year after the operation. This would lead one to believe that the blood creatinine did not possess the same prognostic value in cases of this type as in chronic interstitial nephritis.³ In this connection it is interesting to note that Campbell (14) has called attention to a case of bichloride poisoning that gave a blood creatinine of 12.5 mgm. with ultimate recovery. By way of contrast to the other cases in the series, the findings in the last two cases may be noted as typical of the last stages of nephritis.

W. F., a case of bichloride poisoning in which the kidneys were decapsulated, presents some very interesting information. This case showed a very pronounced retention of all the non-protein nitrogenous constituents, the figures for non-protein nitrogen, urea, uric acid and creatinine being decidedly higher than in any case reported by others (15). No urine was passed for the first five days and no appreciable amounts for the first ten days. After decapsulation of the kidneys on the sixth day the renal activity appeared to improve, and at one time it had sufficiently recovered to cause a reduction in the concentration of the creatinine from 33.3 to 14.8 mgm. per 100 cc.; but with the decline of the patient, the kidneys became less active and the creatinine again increased. The quite favorable output of total nitrogen was insufficient at any time, however, to reduce materially the non-protein and urea nitrogen of the blood, despite the favorable influence on the uric acid and creatinine. Although the highest concentration of uric acid and creatinine, as well as very high figures for non-protein and urea nitrogen, were found on November 20, uremic symptoms did not develop until a week later. This is in harmony with the current view that uremia is not a result simply of the retention of these nitrogenous waste products. It should also be borne in mind in this connection, that death in nephritis is not infrequently due to an acidosis rather than to a uremia (16):

³ This patient died during the week of February 24.

TABLE 4
*Blood and urine analyses in case of bichloride poisoning with bilateral decapsulation**

DATE 1914	BLOOD ANALYSES							DATE 1914	URINARY ANALYSES, DAILY AVERAGES						
	Total solids	Total N	Non-protein N	Urea N	Uric acid	Creatinine	Creatine		Specific gravity	Total N	Uric acid	Creatinine	Creatine	Chlorides as NaCl	Phosphates as P ₂ O ₅
	grams	grams	mgm.	mgm.	mgm.	mgm.	mgm.			grams	gram	gram	gram	grams	grams
	Per 100 cc.								Volume						
	cc.								cc.						
November 13.....	17.9	3.04	219	100	7.7	21.4	19.3	November 16....	195	1.016	0.72	0.08	0.19	0.04	0.34
November 16.....	17.8	2.66	258	183	11.1	27.7	19.4	November 17-18	487	1.015	2.39	0.16	0.33	0.12	0.26
November 18.....	18.1	2.67	267	192	14.3	32.0	20.2	November 19-20	900	1.012	4.83	0.27	0.69	0.19	2.43
November 20.....	18.4	3.10	338	240	15.0	33.3	19.4	November 21-23	997	1.012	6.10	0.30	0.88	0.32	1.84
November 23.....	18.7	2.68	337	219	14.7	28.1	23.2	November 24-25	1188	1.012	7.86	0.43	1.08	0.45	2.30
November 30.....	15.4	2.65	337	240	10.0	14.8	25.1	November 26-30	872	1.012	6.77	0.35	0.89	0.42	1.04
December 5.....	18.4	3.10	368	308	11.2	17.1	20.2	December 1-4	712	1.014	4.38	0.24	0.66	0.28	0.53

W. F., aged twenty-five, took 7 three grain tablets of bichloride of mercury five days before admission on December 13. A double decapsulation of the kidneys was performed on this date under gas, ether and chloroform. On admission the blood pressure was: systolic, 155; diastolic, 70. The characteristic urinary findings throughout were: approximately 0.16 per cent of albumin, few hyaline and granular casts. Symptoms of uremia developed on November 28. On December 2, an infusion of one liter of physiological saline was given.

* Reported also *Jour. Biol. Chem.*, 1915, xx, 391.

Blood analyses on other cases of bichloride poisoning have been reported by Foster (17), Underhill (18), Woods (19), Cohen and Bernhard (20), Lewis and Rivers (21) and Campbell (14). The analyses in the present case, however, are more complete than in any other case reported. It may be noted that of Campbell's two cases, one had a creatinine of 12.5 mgm. and recovered, while in the non-fatal case reported by Cohen and Bernhard, the creatinine reached 9.3 mgm. This is of interest in view of the conclusion reached by Myers and Lough (3) regarding the prognostic value of the creatinine in chronic nephritis. In their series they found that cases with over 5 mgm. of creatinine uniformly terminated fatally.

DISCUSSION

In the present series of cases emphasis has been placed particularly upon the usefulness of the urea nitrogen estimation. A few remarks may be made regarding the other determinations recorded in the tables. The data on the blood uric acid do not admit of easy interpretation, although it may be noted that the uric acid figures are high in quite the majority of the prostate cases.

Since an appreciable retention of creatinine does not occur until the impairment in renal function is advanced, it would appear from the present series of observations to be of decidedly less value as a pre-operative test than the urea, although a high creatinine, when found, would indicate the inadvisability of operating. It may be worthy of note, however, that in the prostate series, the seven cases showing 3.5 mgm. or more creatinine were all among the cases that died. As was pointed out in the introduction, the normal creatinine concentration of whole blood is probably not over 2 mgm. per 100 cc. In this connection attention should probably be called to the recent papers of Hunter and Campbell (22). They have inquired into the accuracy of the values given for the creatinine of normal blood. Their data tend to show that the figures ordinarily reported for whole blood are too high, owing to an interference in the color development by some constituent in the corpuscles. In a series

of normal individuals they found a creatinine content per 100 cc. of 1.7 mgm. for laked blood and 1.1 mgm. for plasma. Granting the correctness of these observations, the data on the whole blood probably possess nearly as great comparative value as on the plasma. With the rise in the creatinine concentration, the disturbing influence of the substance in the corpuscles obviously becomes proportionately less, so that the absolute accuracy of the test increases with its clinical importance.

From an inspection of the blood sugar data, it will be observed that there were several cases in which the determination was of special diagnostic significance (diabetes). Excepting these cases, a few others will be found showing blood sugars appreciably above normal (those above 0.16 per cent), in which glycosuria was not noted. Some of these are associated with the retention phenomenon of advanced nephritis, but a few would appear to be mild cases of diabetes in which the condition had not been disclosed by the urine examination. Comment has already been made on the CO_2 -combining power of those cases showing significant figures.

SUMMARY

Chemical blood observations are reported on a series of fifty-eight cases with prostatic obstruction. The blood urea has been found to be an extremely valuable pre-operative prognostic test in these cases—in our hands more valuable than any other. Cases showing urea nitrogen figures under 20 mgm. per 100 cc. of blood may be regarded as good operative risks so far as the kidneys are concerned. When the urea nitrogen figures are found between 20 and 30 mgm., and especially between 25 and 30, the patient should be operated on with considerable caution and best after a period of preliminary treatment directed to relieve the nitrogen retention. The gas-oxygen method is the anesthesia of choice. The data here recorded indicate that with urea nitrogen figures over 30, the operative prognosis is bad.

Blood analyses are also reported and discussed on seven nephrectomy cases, one case of bichloride poisoning with double decapsulation of the kidneys and nine miscellaneous cases.

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THE OPERATIVE TECHNIQUE OF LITHOTOMY IN THE EIGHTEENTH CENTURY¹

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As is my wont, I shall confine this first lecture of my course on the history of the healing art to the discussion of some special subject of importance which forms an interesting episode in medical annals. Upon the present occasion I have chosen the technique of the operation of lithotomy as it was developed some two centuries ago and as this operation was a very common and much discussed one among the learned operators of the eighteenth century in France, England and Italy, you can readily understand that the subject is not devoid of interest.

To illustrate the description of the various techniques, I place before you two plates taken from Bertrandi's "Trattato della Operazioni di Chirurgia," published in 1763, as they well depict the principal lithotomy instruments of the epoch and as a number of illustrious surgeons will be referred to in this lecture, I here present a list of names of the more noted ones, with the dates of birth and death of each, as well as the city in which he practised.

Paris	{	Baseilhac, Jean, called "Frère Cosme." 1703-1781.
	{	Le Cat, Claude Nicolas. 1700-1768.
	{	Ledran, François. 1685-1770.
	{	de Lafaye, Georges. Died at advanced age in 1781.
	{	Louis, Antoine. 1723-1792.
London	{	Bromfield, William. 1712-1792.
	{	Cheselden, William. 1668-1752.
	{	Sharp, Samuel. 1700-1778.
	{	Hawkins, Caesar. 1711-1786.

¹Introductory lecture to the course on the History of Medicine at the University of Geneva for the Academic year 1917-18, delivered November 7, 1917.

Albinus, Bernhard Siegfried. 1697-1770. The family name was Weiss, hence Albinus. He professed anatomy and surgery at Leyden for half a century.

Italy	{	Alghisi, Tommaso. 1669-1770. A very noted lithotomist and lecturer on surgery at Pisa.
		Bertrandi, Ambrogio. 1723-1765. Professor of surgery at Turin.
		Pallucci, Guiseppe. 1716-1797. Practised at Florence, afterwards at Vienna.

The epoch in which the operation of lithotomy was developed to a high degree of technical skill may be roughly placed between the years 1725 and 1775. The most celebrated lithotomist of France of the seventeenth century, perhaps the most celebrated in all Europe, François Tolet, had died on August 9, 1724, leaving as a legacy to the surgical world his famous work, although in reality a small volume, entitled "*Traité de la lithotomie*," the first edition of which appeared in 1681 and went through six editions, the last being issued in 1722, and with it we take up the thread of the present discourse.

The great lithotomist, Tommaso Alghisi says in his work "*Litotomia, overo del cavar la pietra*," etc., published at Florence in 1718, that "lithotomy is one of the most difficult and dangerous operations performed on the human body and nothing should be neglected which can in any way facilitate the understanding and performance" (of the operation).

Referring now to plate 1, figures 4 and 5 which represent two knives that were devised by Le Cat, you will notice that they each present a groove (*c*). The patient was placed in the usual lithotomy position and a grooved staff of the English pattern (see plate 1, fig. 3) was introduced. You will notice that this grooved staff is quite similar to the modern one devised by Ferguson, excepting that its curve is considerably greater. The staff introduced was then inclined to the right and brought as far as possible towards the perineum. The scrotum being raised by an assistant, the surgeon seized the handle of the staff and after having exactly determined its situation and direction in the perineum the skin and fat were incised with the grooved knife as

in the operation of lateral lithotomy by a long incision which began at the membranous urethra under the pubis and was carried obliquely up to the anus. When this had been done the surgeon felt with the finger the position of the staff under the pubis and then inserted the point of the knife into the membranous urethra and into the groove of the staff. The knife was then carried by a stroke nearly to the prostate.

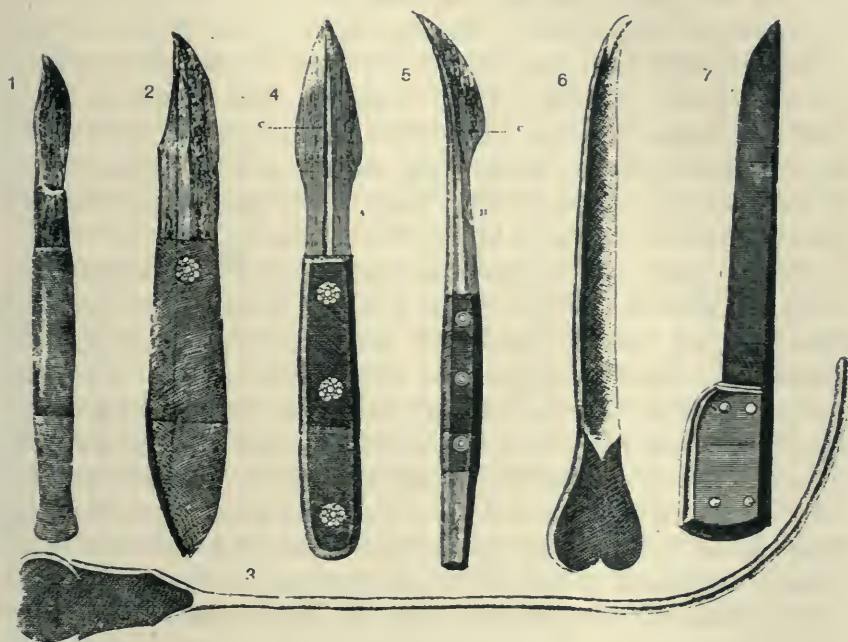


PLATE 1

But Le Cat fearing that it was risky to penetrate as deep as the prostate with the same knife (*A*), directed its point upwards and had it firmly held in this position by an assistant, while the second knife (*B*) was placed in its groove and was thus conducted down onto the staff. Then the first knife (*A*) was withdrawn while the second (*B*) was made to cut from above downwards and inwards towards the bladder, the prostate being incised and probably also a small opening made in the bladder as well.

Now in this technique of Le Cat, in order to incise the prostate with ease, it was necessary to carry the staff further backward and inward in order to reach the gland, when division of the urethra was made in a downward direction by the same knife. After sufficient dilatation the knife and staff were raised up and a conductor was introduced into the bladder along the groove of the staff.

In a letter² addressed to Guattani by Pierre Tarin, the latter proposes the use of a staff whose groove is less open at its distal end and with the edges turned inwardly so that the resulting groove is quite narrow. Tarin made the first incision with an ordinary knife and then introduced another similar to the one represented by figure 2, excepting that its point was turned upward and olive tipped. This knife was used for incising the prostate on the staff as in Le Cat's technique.

Ledran made a very complete and painstaking study of the various methods of lithotomy and finally concluded in favor of the following technique and at the same time observed that at his hands it was always successful, even in the case of very large calculi. After the grooved staff had been introduced and the perineum made tense over it, the integuments were incised with either of the knives depicted by figures 1 and 2. The membranous urethra was divided as in Le Cat's operation but when this had been done, Ledran pushed the tip of the staff upwards by a finger introduced in the rectum and pressure was made over the pubis, while at the same time the handle of the staff was inclined towards the right groin so that the groove at the tip would face the space between the anus and the tuberosity of the left ischium.

Ledran's aim was to incise only the bulbous urethra and he maintained that by making it on the left the rectum would not be injured. When this incision was made the point of the knife was pushed along the curved portion of the staff up to the spot where the latter instrument became directed towards the upper part of the perineum, at which stage of the operation it was con-

²This letter was published in Haller's collection, vol. iv.

fided to an assistant. Next a large grooved director (see plate 1, fig. 4) with a tip similar to that of a conductor, was slipped along the blade of the knife up to the groove in the staff. The tip of the director was passed into the bladder along the groove in the staff and then the latter instrument was withdrawn. The grooved side of the director was next turned so as to face the space between the anus and the tuber ischii and then another knife (see plate 1, fig. 7) was pushed along the grooved director, continuing the first incision in the urethra until the prostate was split on the left side by inclining the staff slightly forward.

Pallucci caused some astonishment among the French surgeons when he published his personal technique in 1757, based apparently on considerable experience. At all events he certainly had studied the subject of lithotomy very carefully. He used the same grooved staff and made a lateral incision in the integuments with a knife rather smaller than the one figured in plate 1, figure 2, while the point was sharper. The groove in the staff was next sought for and when found the knife was abandoned and a trocar was pushed by its tip along the grooved staff between the urethral bulb and prostate. Pallucci points out that one can easily distinguish the urethral bulb with the index finger inserted beyond the tip of the trocar. When the latter instrument had been engaged in the groove of the staff it was then given to an assistant to hold and, since the body of the trocar possessed a furrow made in its under aspect the tip of the knife could be carried to the groove in the staff along this furrow. Then withdrawing the trocar the surgeon continued to incise deeply from above downward until the prostate and vesical neck and a portion of the bladder itself had been divided.

The writings of Gunz referring to Le Cat's and Ledran's operations need not detain us as they are tiresome and of no particular historic value.

The techniques so far described are in reality nothing else than the greater apparatus made lateral and among the difficulties of the greater apparatus which surgeons experienced was perhaps above all the insufficient curving given to the staff.

Albinus who was Rau's pupil described his master's technique and maintained that it was far superior to any other on account of the kind of staff employed. Now Rau did use a longer curved staff with which he could enter the bladder more easily and deeply, while the knife could likewise attain the bladder with greater ease and without wounding the gut.

The handle of Frère Jacques' staff made a right angle with the convex portion so that this part, of necessity, projected more outwardly and even lower through the perineal structures. It was likewise on account of this very great convexity that Frère Jacques could only incise under the pubic commissure and occasionally he was unable to reach far enough backwards, although Mery who witnessed his operations at one of the Paris hospitals stated that the incision could not be more precise or exact.

Both Rau and Cheselden were unable to do it otherwise and it would appear that Frère Jacques did not always finish his operations as well as might have been desired, because his staff was too short and also because it had no groove so that the knife was apt to slip away from the instrument.

In point of fact, Frère Jacques simply performed the operation by the greater apparatus and since the Parisian surgeons were far more dextrous than he in carrying out this technique, it is evident that they could only look upon his methods as merely those of irregular practice bordering on charlatanry.

In the description of Rau's operation as given by Albinus, it appears that the surgeon held the staff himself and never inclined it to the side for the purpose of carrying the knife backwards and inwards, and although his success in this operation may have been real, it does not seem that he in any way improved upon the technique of the greater apparatus excepting that he made a deeper and lower incision and carried it more to the left, a feat he was able to accomplish because his staff was given a very long and full curve.

Later on the French surgeons advised inclining the staff to the side in order to allow the operator to cut more deeply. The reasons for this are explained by Bertrandi who was certainly in a position to know as he had been the eye witness to the work of

the best surgeons in Paris.³ He states that there were two reasons. The first was because they always began the incision too high up, both of the skin and the urethra. The second was because they never carried it down to the anus. Therefore in order to prolong the incision in the integuments they were obliged to incline the staff on which they guided their knife in order to complete it. Now all this difficulty might have been avoided if a fuller and longer curve had been given to the staff.

I would point out that the above technique was not always followed by the desired results. The incision was frequently insufficient for the removal of a good sized calculus, so that the structures were often considerably contused and as it was inadequate for drainage of the bladder, urinary infiltration occurred with all its dire consequences.

Bertrandi tells us of an interesting visit he paid Mr. Sharp at London. One day when this celebrated surgeon was to perform a lithotomy, he asked Bertrandi who was present how long it took the Paris surgeons to perform the operation. To the reply that they could and did do it in from five to eight minutes, Mr. Sharp took out his watch and then performed the operation in one minute. Bertrandi says that he has seen both Hawkins and Bromfield do it in the same time and that this was likewise true of Cheselden and he remarks that on account of the complicated techniques of Le Cat, Ledran and Pallucci these surgeons could never perform the operation with such rapidity.

Bertrandi says further that on account of the insufficient length and especially the depth of the incision many more patients died at the hands of the French operators than those operated on at London. If I refer to Bertrandi so frequently, it is merely because he himself was a very distinguished and learned surgeon and had enjoyed very great opportunities of observation by his long visits to Paris, London and other cities; therefore his critical remarks on the surgery of his time may be considered very au-

³Bertrandi states that he had seen de Garengot, Moreau, Foubert, Tris, Lédran, de Lafaye, Lesne, Louis, Andouille and Fauvar perform lithotomy, therefore the elite of the surgical profession of Paris in his day.

thoritative, although I am perfectly well aware that his name is not familiar to most medical historians.

At one time Bamber and Cheselden attempted to perform Rau's operation as described by his pupil Albinus, but they were never able to reach the fundus of the bladder with Rau's staff. For this reason they resorted to the use of a syringe having a groove on the back for filling the urinary reservoir with water, their object being to cause the viscus to bulge into the perineum.

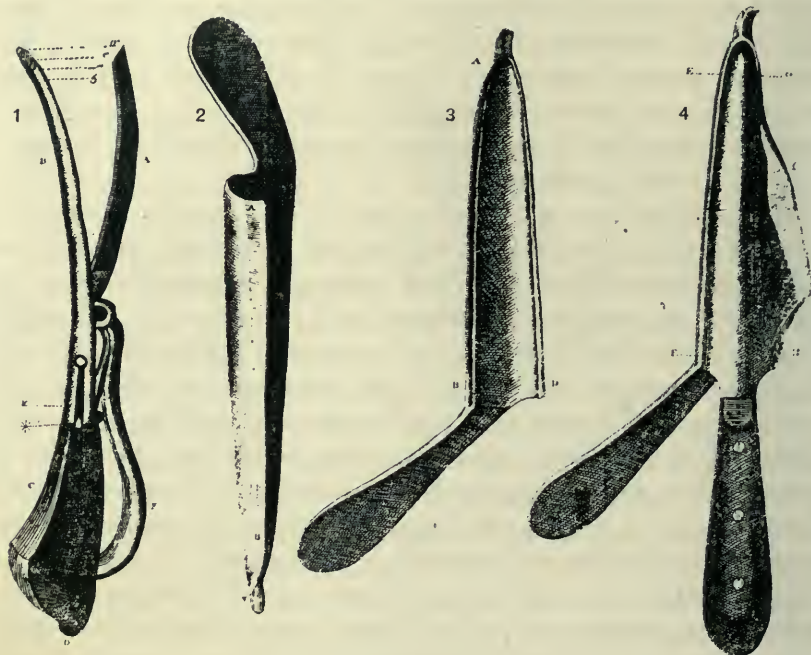


PLATE 2

After the bladder had been distended a ligature was placed around the base of the penis. These attempts were unsuccessful as the patients were unable to withstand the pain of the distended bladder and in a very large number of cases, the bladder had undergone pathologic changes which prevented it from becoming distended. Therefore this technique was soon given up and these operators returned to the incision through the prostate for entering the bladder.

It would also appear that many surgeons readily discovered that when the incision into the bladder was made so low down and so deeply there was great risk of injury to the rectum and the production of false passages between the gut and the fundus of the bladder, the inevitable result being the formation of abscesses, sinuses and fistulae.

However in 1743 Foubert⁴ published a technique of his own by which he thought the fundus of the bladder could be reached without incising the vesical neck or urethra. He was well aware of the disadvantages of distending by injecting water into it, so in order to produce a gradual increase in the capacity of the organ, he ordered his patients to drink copiously of an emollient decoction and then to retain the urine as long as possible, all this being done for some days previous to the operation, and then on the morning of the day chosen for the interference the patient was to drink still more freely of the fluid. When the bladder was considered sufficiently distended, some means of compression was applied to the root of the penis and the patient being placed in the lithotomy position, an assistant pressed upon the bladder with a cushion above the pubis so that the fundus would be pushed down to the perineum and present a larger surface to the operator. The left index finger was then introduced into the rectum in order to draw the gut to the right, while with the right hand a trocar measuring 12 to 14 cm. in length, with a groove on the back, was thrust in about an inch above the anus on the left quite near to the tuber ischii. When the urine flowed along the groove of the instrument it was withdrawn slowly so that its point should not injure the bladder walls. Then with a knife similar to that figured in plate 1, figure 1, but with a longer blade which was fixed at a very obtuse angle to the handle, the structures were incised obliquely by directing the blade along the groove in the trocar and the fundus of the bladder opened.

Experience showed that the patients were unable to dilate the bladder by the ingestion of the decoction to a sufficient degree

⁴*Nouvelle Methode de tirer la Pierre de la Vessie. Memoires de l'Academie royal de Chirurgie, Tome 3, p. 255.*

and that for this reason there was much danger of incising along side the organ and not into it, or even cutting the vas deferens and seminal vesicle.

I now come to the operation devised by Frère Cosme with his famous *lithotome Caché* which is represented by figure 1, plate 2, and hardly needs further explanation. You will observe however that there is a sliding screw which regulates in degrees the amount of projection given to the blade. After an ordinary grooved staff had been introduced into the bladder and held by an assistant in the position for lateral lithotomy, the surgeon incised the skin and fat, beginning at the side of the raphe and extending down to the tuber ischii. In adults the incision would be about $2\frac{1}{2}$ inches long. Then the point of the knife was engaged in the groove of the staff and a small slit was made in the urethra and through this the tip of the lithotome was introduced closed. The staff was then inclined forwards and the lithotome was pushed along into the bladder. The blade of the lithotome was then made to protrude to the desired extent and the instrument withdrawn following the direction of the incision in the soft structures.

Frère Cosme had such confidence in his instrument that he said any one could perform the operation. Now in lithotomy everything depends upon the division of the prostate and it is evident that the only advantage in Frère Cosme's technique was that he obtained a greater dilatation of the opening into the bladder by the use of his lithotome.

I would point out that the lithotome caché was nothing else than a slight modification of the *bistouri caché* employed in that epoch for the operation for hernia. The great danger of this instrument was that during its withdrawal it was apt to injure the rectum, seminal vesicle or vas deferens and that such accidents did occur we know from reports to that effect which were published in this epoch, particularly by Louis and Le Cat.

In order to eliminate the danger, Cacqué suggested constructing the blade with a dull point. However this did not seem to improve the instrument and patients died from hemorrhage of the internal pudic artery at the hands of Frère Cosme himself, as well as in the practice of other skilled surgeons.

A surgeon of the Bicêtre Hospital, Thomas by name, undertook to improve upon Foubert's and Frère Cosme's operations. He proposed employing a trocar similar to Foubert's but with a lance-shaped point, the cannula which offered a slit along its side containing a blade which by a proper mechanism could be made to protrude to the desired degree. The bladder was distended with fluid and pressed down upon from the suprapubic region by an assistant, the trocar was pushed into the bladder just to the *side of the middle line and at a point one finger's breadth below the pubis*. Then when the urine flowed the instrument was turned somewhat obliquely towards the tuber ischii, causing the blade to project to the desired degree and the instrument was withdrawn, the conductor with which the instrument was provided being retained in the bladder so that the forceps could be immediately introduced along it for the removal of the calculus.

Bertrandi says that the first time he saw Cheselden's incision made it was done by Bromfield whose operations were as successful as those of Cheselden. When Bertrandi showed Bromfield the lithotome caché of Frère Cosme, he laughed and said that the instrument "was devised for surgeons who did not know how to operate."

At this epoch Mr. Hawkins had just devised a conductor (see plate 2, fig. 2) whose left edge was a cutting one (*AB*) and with it he split the prostate on the side after first having opened the urethra. In other words Hawkins incised the skin and fat as in lateral lithotomy and then opened the urethra as near as possible to the prostate, after which the conductor was introduced into the groove of the staff and turning the cutting edge obliquely downwards, the prostate was incised.

At the same time Mr. Bromfield had invented a conductor with two lateral grooves (see plate 2, fig. 3) in which a second conductor (see plate 2, fig. 4) could be pushed and which fitted so well into the grooves that it practically made one instrument. It also had a cutting edge on the left.

However during the entire summer that Bertrandi passed with Mr. Bromfield, he never saw him use his conductor, always making a lateral incision of the prostate on a grooved staff after

the technique of his master, Cheselden, and always with ease and success.

You will see gentlemen what attention was given to the operation of lateral lithotomy by the surgeons in the middle of the eighteenth century but from all I have read on the subject in the original memoirs and books published at the time, I unhesitatingly conclude that the most skilled operators employed the simpler methods and instrumentation and that their results were by far the best.

25

THE EMPLOYMENT OF THE HIGH FREQUENCY CURRENT FOR THE EXTRACTION OF CALCULI INCARCERATED IN THE LOWER END OF THE URETER

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Various methods have been proposed for the extraction of calculi in the terminal intravesical portion of the ureter. In 1903¹ the writer made an exhaustive study, and presented one case in which he was able to extract a calculus incarcerated in the lower end of the ureter by means of a ureteral catheter, and also mentioned cases in which stones had been removed from this portion of the ureter by suprapubic cystotomy. Since this time several articles have appeared detailing various cases in which, by means of dilating instruments, forceps or scissors, calculi have been extracted from the lower end of the ureter intravesically. Bransford Lewis has been one of the most frequent contributors on this subject.

The technique which is presented herewith consists in the employment of the high frequency spark to incise the mucous membrane covering the incarcerated calculus, thus enlarging the ureteral orifice to a degree sufficient to permit its passage into the bladder.

Case 1. No. 4390, aged 29, was admitted May 22, 1915, complaining of recurring attacks of colicky pain in the lower portion of the abdomen on the left side. Ureteral catheterization had been carried out elsewhere in December, 1914, following which he passed a small stone.

On cystoscopic examination there was marked enlargement of the left corner of the trigone and left ureteral ridge, both of which were very prominent. The picture at once suggested an incarcerated calculus in the intravesical and intramural portions of the ureter, notwith-

¹The surgery of the lower ureter. *Annals of Surgery*, 1903, xxxvii, p. 668.

standing the fact that the plain X-ray revealed no shadow in this region. Attempts to pass a ureteral catheter were unsuccessful and it occurred to the writer that it would be possible to enlarge the ureteral orifice by fulguration of the mucosa which was stretched tensely over the stone. This was accordingly done and a linear burn made, starting at the ureteral orifice and extending along the line of the ureteral ridge for a distance of about 1.5 cm. Following fulguration there was some vesical



FIG. 1. SCHEMATIC VIEW OF BLADDER

Showing marked bulging of intramural portion of ureter due to incarcerated stone. Cystoscope and fulgerating wire in place.

irritation but no definite pain in the kidney, ureter or testicle. Three days after the treatment there developed considerable urinary urgency, frequency and pain at the end of urination. These symptoms continued for two days, when the patient passed through the urethra a calculus, measuring 4 by 6 by 8 mm. This was accompanied by slight hemorrhage, the first he had noticed. There was no hematuria subsequently and the pain which had been present in the region of the kidney ceased. The patient was discharged eleven days after fulguration, free from symptoms and able to retain urine for eight hours.

Case 2. No. 5411, aged 36, was admitted October 3, 1916, complaining of stone in the right ureter. He had had intermittent attacks of pain for almost three years, the pain being typical of ureteral colic, beginning in the right side and radiating into the right groin and testicle, and was accompanied by occasional hematuria.

The X-ray examination revealed a large ureteral calculus in the terminal portion of the ureter. On cystoscopy, the right corner of the trigone and right ureteral ridge were considerably enlarged and oedematous. The ureteral orifice was small and round, and from it was seen protruding a portion of a black irregular calculus. A ureteral catheter was passed and an unsuccessful attempt made to dislodge the stone. The high frequency was then directed to the mucous membrane and a linear burn 1 cm. in length made, beginning at the orifice and extending upward to the limit of the prominence caused by the calculus. On the fourth day after fulguration, X-ray examination showed the stone in the same position. The patient had had considerable vesical disturbance, with retention of urine on three occasions. On the sixth day, the stone was passed "without the slightest pain," according to letter from the patient. He was heard from nine months later at which time he was free from symptoms.

Case 3. No. 3935, aged 24, was first admitted May 16, 1914, complaining of intermittent attacks of pain in the back and testicles. X-ray examination revealed the shadow of a stone in the right ureter just below the uretero-pelvic junction; the remainder of the examination was quite negative. On May 29, 1914, a lumbar uretero-lithotomy was performed and the calculus removed. The patient was practically free from symptoms until September, 1916, when he began having attacks of renal colic, on the left side, the pain radiating into the testicle. These attacks were always followed by the appearance of blood in the urine. On X-ray examination a definite shadow was seen in the region of the lower end of the ureter. On cystoscopy, December 30, 1916, the left ureteral orifice was apparently normal and the ureteral ridge was quite prominent, the mucous membrane bulging, as shown in the accompanying illustration. A ureteral bougie armed with a waxed tip was passed into the left ureteral orifice and a definite scratch obtained. A linear burn 1 cm. in length was made, extending from the ureteral orifice upward and outward in the direction of the ureteral ridge over the prominence produced by the calculus. January 8, 1917, the patient passed a stone measuring 1 cm. in length and 4 mm. in diameter, slightly rough and composed entirely of calcium oxalate. On cysto-

scopy, February 17, 1917, the left ureteral orifice was somewhat elongated and of irregular shape but functioned normally. The right ureteral orifice was circular, pinpoint in character, evidently slightly constricted, and the ejection of urine was accompanied by a slight ballooming above it.

CONCLUSIONS

The employment of the high frequency current in cases of calculus, incarcerated in the intramural and intravesical portions of the ureter, is successful in enlarging the orifice sufficient to permit its passage. Furthermore this operation is simple, can be carried out without anaesthesia, and does not produce more than slight hemorrhage.

57

PRESENTATION OF DEVICE FACILITATING THE INTRODUCTION OF THE CYSTOSCOPE IN CERTAIN DIFFICULT CASES

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From The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital

While the passage of the cystoscope in the majority of cases is a very simple operation, every cystoscopist experiences difficulty from time to time in the introduction of the instrument in certain cases of urethral stricture and in those distortions of the urethra resulting from extra-urethral infections, various operative procedures and congenital malformations. It is usually possible by means of filiform and follower to effect an entrance into the bladder, following which the cystoscope may be introduced without difficulty. In certain cases however even after preliminary dilatation, satisfactory instrumentation may be impossible. This difficulty is occasioned not so much by the area of actual fibrosis as by those irregularities and false passages which are occasionally encountered behind the site of the stricture. Frequently in these cases it may be possible to dilate the urethra to its normal calibre, following which an instrument of smaller size cannot be introduced. In a recent case requiring cystoscopy examination revealed an extensive fibrosis involving the bulbous and membranous portions of the urethra. By means of filiforms and followers the stricture was dilated to 28 French, following which numerous attempts to pass a cystoscope were unsuccessful, the point of obstruction being in the prostatic urethra.

The ease with which the filiform and follower is passed in most cases, even after failure by the ordinary methods of instrumentation, suggested the possibility of utilizing the filiform in these difficult cases as a guide to the cystoscope.

The device herewith presented consists of a metal truncated cone, the base of which is cupped out to conform with the curved

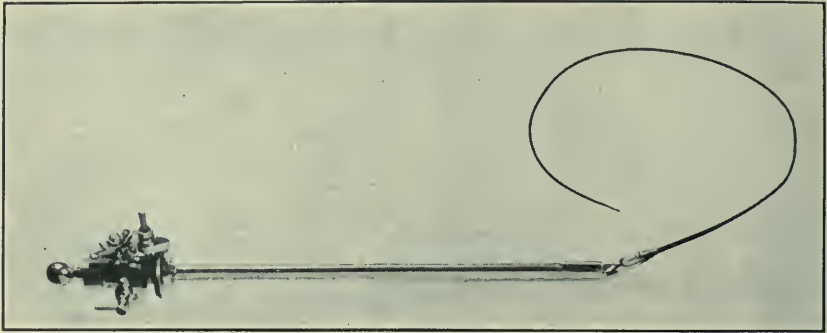


Fig. 1. View of Brown-Buerger Cystoscope with Metal Lamp Attachment and Filiform.

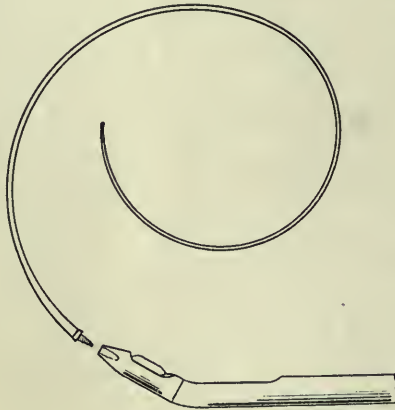


Fig. 2. Sagittal View of Terminal End of Cystoscopic Sheath with Metal Attachment and Filiform.

surface of the distal end of the ordinary cystoscopic lamp and is firmly secured to the metal of the lamp by solder. The terminal end of the attachment is drilled and tapped so as to receive the screw end of a male filiform.

In operation the filiform is passed into the bladder after which the cystoscope armed with the lamp with conical attachment is fastened to it and the instrument is introduced as the ordinary follower. In cases of urethral stricture it would seem advisable to carry out preliminary dilatation by the usual methods, after which, if the cystoscope cannot be passed, the plain lamp can be replaced by this modification and the instrumental difficulty overcome.

It should be emphasized that this method is not proposed to supplant urethral dilatation in cases of urethral stricture but rather to avoid the trauma which necessarily accompanies repeated attempts to introduce the cystoscope in those cases of urethral distortion and irregularity frequently associated with stricture or, as has been indicated above, following operations on the urethra or resulting from extra-urethral infection.

A requisite to the successful operation of this method would seem to be moderate distension of the bladder before attempting instrumentation, either by means of irrigation or by instructing the patient to hold his urine for some time previously. In one of our cases in which this procedure was overlooked the filiform coming in contact with the anterior bladder wall broke just behind the attachment of the screw. The accident however can be avoided by preliminary filling of the bladder.

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Journal of Management Studies, 19(1), 67-80.

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ON THE ABSORPTION OF DRUGS AND POISONS FROM THE BLADDER AND THE URETHRA

I. ABSORPTION OF APOMORPHIN AND MORPHIN

DAVID I. MACHT

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James Buchanan Brady Urological Institute, Baltimore*

A large number of drugs is employed in genito-urinary practice in the treatment of the bladder and the urethra: some as antiseptics, some as styptics, some as local anesthetics and sedatives and still others as stimulants of the mucous membranes and for other purposes. The general belief among the profession is that the drugs or reagents thus exhibited or administered exert a purely local or topical effect, and that absorption from the bladder or urethra into the systemic circulation is rare and, if taking place, is but slight in degree and of no practical importance. In connection with an investigation concerning the absorption of various drugs and poisons through devious and unusual channels or portals of entry such as the eye, the vagina, etc. (1), the author has undertaken an inquiry into the possibility of systemic absorption of pharmacological agents and the degree of such absorption in various parts of the urinary tract. The results have turned out to be of considerable interest not only from the purely pharmacological but also from the practical clinical point of view, and it was therefore deemed desirable to report them in this place. In the present communication the problem of absorption from the bladder and urethra will be taken up. In a later paper the question of absorption from the ureters and the pelvis of the kidney will be dealt with.

METHOD

In the present research the study of absorption from bladder and urethra was confined to male animals. Dogs were found to

be ideal subjects for this purpose because, in the first place, the histological structure of the urethra and bladder in the dog is practically the same as that in man, and secondly, because the vesical and urethral sphincters in this animal are so powerfully developed that it is very easy to confine the action of a drug to the bladder or urethra at the pleasure of the experimenter.

If a fine catheter, with a side opening and a wire guide, is passed through the urethra of a male dog into its bladder and is left in position, the internal sphincter contracts so firmly around it that any fluid injected through the catheter into the bladder is practically confined to that cavity alone, and does not permeate into the urethra. Indeed in some dogs it is almost impossible to pass a catheter into the bladder at all on account of the excessive irritability and spasmodic contraction of the sphincter muscles.

If, on the other hand, it is desired to limit the action of a drug to the urethral mucosa only and not to the bladder, all that is necessary is to insert the catheter as far as the external sphincter, in which case a fluid injected through the catheter under moderate pressure will merely irrigate the urethra and flow out again externally without penetrating either the posterior urethra or the bladder. The conditions just described hold good for the great majority of dogs. In exceptional cases, of course, the sphincters may not be so well developed or may not contract so tightly, thus preventing a sharp differentiation in applying the drug to the bladder or urethra.

APOMORPHIN AND MORPHIN AS INDICATORS OF ABSORPTION

In a paper on the absorption of drugs from the eye (2) the author has shown that apomorphin offers a very convenient method of determining the absorption or non-absorption of drugs from various surfaces into the general system in unanesthetized animals. A little apomorphin solution or powder introduced into the conjunctival sac of a dog was shown to be followed in a few minutes by violent emesis. Inas-

much as apomorphin is the best known example of a centrally-acting emetic, the conclusion is inevitable that vomiting in such a dog has been produced by the absorption of apomorphin from the eye through the blood or lymph stream into the general circulation and through its action upon the vomiting center in the brain. In exactly the same manner the author has pointed out that apomorphin is readily absorbed from the vagina (3). Furthermore, inasmuch as the vomiting center of dogs is almost as sensitive to the action of morphin as to that of its derivative, apomorphin, the introduction of morphin salts in solution or in powder form into the conjunctival sac or into the vagina of dogs was also followed by prompt vomiting, again indicating the absorption of the drug from those organs into the general circulation. The same alkaloids were utilized in the study of absorption from the bladder and urethra.

ABSORPTION FROM THE BLADDER AND URETHRA OF APOMORPHIN AND MORPHIN

If a catheter is gently introduced into the bladder of a male dog in the manner described above, and a solution of apomorphin (0.1 per cent to 1 per cent) is injected into the bladder and the catheter left in place in order to prevent regurgitation of the solution into the urethral canal—absorption of the drug as evidenced by emesis, is very slow. The dog generally does not vomit for half an hour or longer and sometimes he does not vomit at all. If now the same animal is used on another day and the same strength of apomorphin solution or even weaker solutions of the alkaloid be employed for the irrigation of its urethra, vomiting promptly follows, generally in from two to five minutes. This marked difference in the absorptive power for apomorphin between the bladder and urethra has been repeatedly noted by the author in numerous experiments with various concentrations of the drug. It occurs irrespective of whether the bladder contains urine or is empty. The following protocols may serve as illustrations:

Experiment of October 11, 1917. Large white dog, weight 10 kilos.

10.05 a.m. Introduced into the bladder 10 cc. of 0.5 per cent apomorphin hydrochloride solution, leaving catheter in place.

10.25 a.m. No vomiting and no defecation

11.00 a.m. No vomiting

12.00 m. No vomiting

Experiment of October 15, 1917. Same dog as above.

11.43 a.m. Soft catheter introduced into urethra as far as the external sphincter. Irrigated gently with 0.1 per cent apomorphin hydrochloride solution for two minutes

11.45 a.m. Salivation

11.48 a.m. Repeated vomiting and defecation

Experiment of May 16, 1917. Medium-sized dog, 6 kilos. Introduced catheter into the bladder and left it in place. Injected 5 cc. of a 1.0 per cent of apomorphin hydrochloride. Vomiting occurs about forty-five minutes after introduction of the drug.

Experiment May 17, 1917. Same animal. Urethra irrigated with 0.1 per cent solution of apomorphin hydrochloride; vomiting occurs in three minutes.

Exactly the same relationship between the absorptive powers of the bladder and urethra was found to hold good in case of morphin except that vomiting generally took place after a longer period of time in case of this alkaloid than in the case of apomorphin. Further discussion of the morphin action need not, therefore, be entered into in this place.

ON THE COMPARATIVE ABSORPTIVE POWER OF THE ANTERIOR AND POSTERIOR PORTIONS OF THE URETHRA

The dog offers us an opportunity not only of studying the comparative absorptive properties of the bladder and urethra, but also enables us to observe to some extent the comparative absorptive power of the anterior and posterior portions of the urethra. This may be done as follows: A catheter with a side opening is passed through the urethra into the bladder, its presence in the bladder being proved by withdrawal of urine with a syringe. Fluid injected through the catheter in this position naturally enters the bladder and does not flow outwards through the urethra. The catheter is now gradually withdrawn

to a point where suction with the syringe obtains no more urine, thus indicating that the tip of the catheter is beyond the internal sphincter. If small injections are made the fluid will remain confined to the posterior urethra but as the amount of fluid is increased, the internal sphincter yields and the fluid passes into the bladder. On the other hand when the catheter is withdrawn so far that its tip extends beyond the external sphincter, fluid injected under moderate pressure will regurgitate and will come in contact only with the anterior urethra. This fact offers us a practical method of applying medicaments to the posterior or anterior portions of the urethra at will, and in this way the comparative absorptive power of these two divisions can be investigated.

By the method above described, the author has found that the absorptive power of the posterior urethra is distinctly greater than that of the anterior. This may be illustrated by the following protocols:

Experiment A, December 31, 1917. Black and white dog, 8 kilos. Posterior urethra is irrigated with 0.5 per cent of apomorphin hydrochloride solution so that the fluid runs into the bladder. Vomiting occurs *four and a half* minutes after the beginning of the injection.

Experiment B, January 2, 1918. Same dog. Catheter introduced as far as but not past the external sphincter and the anterior urethra is irrigated with 0.5 per cent of apomorphin hydrochloride. Vomiting takes place *six and a half* minutes after the beginning of the injection.

Experiment C, January 5, 1918. Same dog. Ten cubic centimeters of 1.0 per cent solution of apomorphin hydrochloride is introduced into the *bladder* and catheter is left in place. Vomiting does not occur within thirty minutes after introduction of the drug.

Experiment 25. Yellow dog, 6 kilos. Irrigation of posterior urethra with apomorphin hydrochloride, 0.5 per cent is followed by emesis in three minutes.

Irrigation of the anterior urethra in the same dog on another day with same solution strength produces vomiting *four and a half* minutes after beginning of injection.

Ten cubic centimeters 1.0 per cent solution apomorphin hydrochloride introduced into the bladder with catheter left in place produces vomiting in twenty-five minutes.

Experiment 26. Yellow and white dog, 10 kilos. Irrigation of posterior urethra with 0.1 per cent apomorphin hydrochloride produces vomiting in five minutes.

Irrigation of anterior urethra on another day with the same per cent solution is followed by vomiting in seven minutes.

Introduction of 10 cc. 0.1 per cent solution of apomorphin hydrochloride into the bladder with catheter left in place is not followed by vomiting for an hour.

DISCUSSION

From the above described experiments it will be seen that the bladder and the urethra differ greatly in their absorptive power for apomorphin and morphin. That this is also true in case of other drugs and poisons will be shown in the next communication on the subject. This difference in the absorptive power between the two organs is, as far as the author has been able to gather from the empirical observations of clinicians, probably also true in clinical experience. How this difference in the absorptive powers between the urethra and the bladder is to be explained is not altogether clear; but the fact that the bladder is devoid of glands on the one hand, and the urethra contains numerous glands, on the other, is probably at least in part responsible for the phenomenon.

Equally interesting both from the scientific and the practical clinical point of view is also the difference in the rapidity of absorption of apomorphin and morphin between the anterior and posterior portions of the urethra. This difference is really more marked than is at first seen from the illustrative protocols given above, for it must be borne in mind that the total mucous surface of the posterior urethra is much less than the total mucous area of the anterior one so that even if vomiting were produced by the same solution in the same time from both portions of the urethra, it could be argued that even in such a case the absorption from the posterior urethra was more rapid. The explanation of this phenomenon is also not quite clear, but it is suggested that it may at least in part be due to the absorption through the prostatic ducts opening into the posterior urethra.

SUMMARY

1. Apomorphin and morphin offer a convenient method for the study of absorption from the bladder and the urethra in the unanesthetized animal.

2. Absorption of apomorphin and morphin from the bladder is very slow.

3. Absorption of apomorphin and morphin from the urethra is very marked and rapid.

4. Absorption from the posterior portion of the urethra is more efficient and rapid than from the anterior.

5. The above observations are of interest not only from a purely pharmacological point of view, but also from the clinical.

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WAR NEPHRITIS¹

P. AMEUILLE

TRANSLATED FROM THE FRENCH BY

HERMAN O. MOSENTHAL

During the years which immediately preceded the war the study of chronic nephritis was productive of significant results. The part played by hypertension and the faulty elimination of chlorides and nitrogenous residue, and the pathological physiology and symptomatology entailed by the retention of these waste products have been elaborated in great detail. The investigations dealing with acute nephritis are relatively few in number, and the description of this disease is much less accurate, because such cases are comparatively rare during times of peace. We know that the acute nephritides may be divided into two groups: *secondary acute nephritis* and *primary acute nephritis*.

The cases of secondary acute nephritis usually manifest themselves either during the course of or following an infectious or toxic disease. In these instances, the relation of cause and effect is clear. The nephritides of scarlet fever, diphtheria, syphilis, pregnancy, and certain other acute intoxications are well known.

The cases of *primary acute nephritis* are independent of any known cause, including those mentioned in the previous paragraph. In order to be certain with which form of acute nephritis we are dealing, it is necessary to eliminate all possible etiological factors, such as intoxications or infections (latent syphilis, mild scarlet

¹ This article was originally published under the title of "Les Nephrites de Guerre," in the *Revue de Pathologie de Guerre*, No. 5 (Vigot, Editeur). It contains much that is of very timely interest and the translation should be an aid to a more thorough understanding of the relation of the present war to nephritis and in furthering an appreciation of the methods by which the French physicians are handling this problem. The proper authorization to publish this article in English has been obtained. Two figures, illustrating microscopical lesions in the kidney, could not be reproduced satisfactorily, and have been omitted.

fever, unrecognized diphtheria). If none of these exist, it is possible to make a diagnosis of "*cryptogenetic*" primary acute nephritis. These are the cases that have assumed an entirely disproportionate importance during the course of the war, and it is to them only that we wish to devote our attention.

In times of peace, primary acute nephritis is generally believed to be the result of exposure to cold. From the clinical point of view, this is a nephritis characterized by a large amount of albumin in the urine, marked edema, often hematuria, and at times, anuria.

It is not very common in the reports of St. Bartholomew's Hospital, dealing with 7000 annual medical admissions. Sir Wilmot Herringham, in summarizing these reports, notes a total number of 166 cases of acute nephritis during a period of nine years. This constitutes about 2.6 cases of acute nephritis for every 1000 medical admissions. If only the male patients of military age are taken into consideration, as we are doing under the present circumstances, the proportion is even lower. Records of the Parisian hospitals show a still smaller proportion. In summarizing the situation, it would seem that people of military age do not give evidence of acute nephritis in more than 2 per thousand of medical cases during times of peace. Since the beginning of the war, this proportion has increased to a very considerable degree. In our first article on the subject, in November, 1915, we estimated that there were more than 1 per cent. of these cases. The incidence of this disease has increased considerably since. It is neither possible nor justifiable at this juncture to give exact percentages, but one can form an estimate from the statistics published up to the present. Including June, 1915, 1062 cases had been observed in the English army. The papers of Abercrombie and Sir J. Rose Bradford deal with more than 500 cases. The latter has himself examined 1450 cases. I have not observed more than 200, although I have had as many as 36 at once in a "service d'ambulance." These figures speak for themselves, and it is not astonishing to see how frequently the prevalence of acute nephritis has impressed those who have been able to observe it. Sir William Osler calls it

"infectious epidemic nephritis," and says that "it is a disease which we have not seen previously." Abercrombie, speaking before the Royal Medical Society, declares that it has caused great anxiety among those who are working on the French front.

In the English army the number of publications regarding this subject are accumulating rapidly. It was first studied in a report of Colonel Beveridge; it has been proposed as a subject for study by the "Medical Research Committee;" it was discussed during an entire session of the "Royal Medical Society." The Imperial and Royal Society of Physicians of Vienna devoted much time to it in the course of the year 1915, and if any opinion can be formed from the number of enemy publications which have reached us up to the present time, the disease is very frequent among them. The first paper published in France is without doubt that of Parisot and myself; this was read before the Academy of Medicine on November 10, 1915. Since then, studies on the subject, published or in manuscript, have been completed at various other parts of the French front.

The large number of cases studied, and the new facts regarding the classification of nephritis, obtained during pre-war times, have cleared up many points in regard to the clinical aspects of acute nephritis. The more important question of etiology is, unfortunately, not as well answered. Many curious facts stand out in the histories obtained from these individuals, but it is not possible to group them so as to make the evidence point towards one or several infections or intoxications as the cause or causes of this disease. The question of ultimate prognosis is still unsolved. This may be attributed to the comparatively recent occurrence of this condition, to the fact that many of these patients have not yet recovered, and also to the lack of coöperation between the different doctors of the armies of the interior. In order to progress, it is necessary first to study the clinical symptoms of war nephritis, and subsequently, after such data have been brought together, to speculate as to its etiology.

From a *clinical* point of view, war nephritis is not constant in its symptomatology; most authors have described a *nephritis with edema*. This is the most common form and the one most

easily diagnosed. Sometimes, however, it passes unnoticed on the first examination (those who understand the actual conditions under which the first examination is made will easily grasp the reason for this). In several descriptions it is pointed out, without insistence on the fact, that *acute nephritis without edema* may exist. These instances are not very frequent, but if they are studied closely, it is found that they have certain interesting peculiarities: they are almost invariably febrile, accompanied by more or less marked signs of uremia, and characterized by difficulty in the excretion of nitrogenous substances. They deserve to be placed in a separate category, under the name of *pure azotemic nephritis*. This qualification is necessary since the cases of nephritis with edema are constantly azotemic, at least, during the first few days of the disease. The difficulty in eliminating nitrogen appears to be fundamental in the pathological physiology of these nephritic patients. It is possible that edema, and at times hypertension, may be superadded in these cases, but I have never found a purely edematous nephritic nor a single purely hypertensive one.

The very few autopsies thus far performed, indicate that the anatomical picture of war nephritis is rather new and particularly interesting. It is, above all, an *acute interstitial nephritis*. In attempting a systematic clinical anatomical classification, one can only regret the uncertainty as to the etiology of these types of nephritis.

The study of war nephritis in this paper will be divided into the following chapters:

1. Acute nephritis with edema.
2. Pure azotemic acute nephritis.
3. Prognosis.
4. Pathology.
5. Etiology.

ACUTE NEPHRITIS WITH EDEMA

Acute nephritis with edema is the most striking clinical form of acute renal disease. During times of peace it constitutes a well-known clinical entity: everyone knows the anasarca of scarlet

fever, the acute edematous nephritis of secondary syphilis, and even (although it may be rare) acute edematous nephritis without appreciable cause, which is supposedly brought about by exposure to cold. The types without edema, of which mention will be made further on, have been less frequently observed.

It is the acute nephritis with edema which has almost entirely monopolized the attention of army physicians since the beginning of the present campaign. Foreign authors mention scarcely any other form of nephritis, and this is true of some French investigators. This proves without doubt that anasarca furnishes certain very striking characteristics on which the hurried or superficial observer concentrates his entire attention. It may also be assumed that it is the form of nephritis the most frequently met with. In my personal statistics, almost 90 per cent of the cases are of this type.

Mode of onset. It is characteristic of the war nephritides that they come on independently of any previous disease and are brought about by no apparent cause. It is for this reason that Parisot and I have described them as *cryptogenetic*. In most instances, no information can be derived from the histories. Nevertheless, I have several times found among my patients that the first symptom dates from a sore throat, occurring in the course of, or following, a fever. It is possible to state that this throat affection was not caused by diphtheria, nor was it secondary to scarlet fever. The doctors of the English army note the frequency of initial bronchitis. Exposure to cold is often spoken of. The German authors consider this a common and important cause. Seventy per cent of the patients observed by Bruns attributed their illness to it, and Chiari claims that it was almost constant among his 230 patients. In my experience, especially during the month of August, this factor did not play as much of a rôle as in the cases of Bruns and Chiari. It must be remembered that at the onset of the disease there is sometimes a period of general malaise, associated with chilly sensations or true chills, from which the patient receives the impression of having been exposed to cold.

Many cases seem to have a febrile onset. Hogarth, in the tables included in his monograph, points out that this occurs frequently. I observed a slight elevation of temperature, a little above 38°C. (100.4° F.) in some patients at the time of admission, but the temperature returned to normal as soon as the patient had remained in bed for twenty-four hours. It may be concluded, therefore, that at the onset of an acute edematous nephritis there is often a febrile period of short duration, which may possibly be a constant factor, and which because of its short duration and of its moderate degree, may often pass unnoticed. If this initial febrile period could be demonstrated as constant, it would constitute a strong argument for the infectious origin of war nephritis. It is probably to this fact that Schneyer alludes when he says that in 70 per cent of the cases there is a brief febrile period before the onset of edema. He regards this phenomenon as indicating the presence of influenza, and seems to consider war nephritis identical with the nephritis secondary to influenza. Inasmuch as the description of influenza has been applied to a large group of febrile diseases, which have not been definitely classified, the opinion of Schneyer is of no more than passing interest.

Very frequently the onset of acute edematous nephritis is characterized by pain. The patient remembers having had a headache—or at least his head felt heavy—pains in the lumbar region so severe that they interfered with his ability to carry his pack, or muscular pains in the limb, especially the legs. Consequently the soldier falls out of line, being completely prostrated.

Others, however, are affected first with respiratory disturbances, dyspnea on exertion, or attacks of paroxysmal dyspnea. In the English army, the onset has frequently been characterized by bronchitis with a dry cough, a phenomenon which I have never encountered; and also by a pseudo-peritoneal onset, with abdominal pain and vomiting, which I have observed on only one occasion, and this in an English soldier. In some instances, the first symptom noted is hematuria; this, however, is often not reported to the physician in charge. It is almost invariably the edema which first attracts attention, particularly the edema of the

face, which is so prominent that the usual course of events is as follows: On awaking, the patient feels his face drawn, has trouble in opening his eyes, and when he goes out into the light his companions make fun of his curious change of countenance. At the onset the swelling almost always disappears by degrees during the course of the day, to reappear the next morning, and it is sometimes only at the end of two or three days of edema that the soldier consults a physician. The examination of the urine reveals a marked albuminuria and the patient is invalided to the rear.

Analysis of symptoms. Edema. Edema appears most frequently in the face; at least, it is here that the men as a rule first notice it. Possibly the other parts of the body may escape observation, since the men take off their clothes only at rare intervals. It involves the cheeks, the tissues about the eyes, and often the eyelids. At the onset, also, the external genital organs often show a transient edema. The parts which are distended to the greatest degree, and in which the swelling lasts the longest, are the lower limbs and the lumbar region. In the most pronounced cases, the arms are also involved, and the backs of the hands and the fingers are swollen. The edema of acute nephritis is soft, and on compression shows a deep and persistent pitting. It is a pale edema, and in the legs this characteristic serves to distinguish it from other forms of edema occurring under present conditions. The edema accompanying frozen feet is, at least during the inflammatory stage, red, fairly hard, thick and painful. In the face, as well, the edema of this form of nephritis is pale. It is particularly during reabsorption of the swelling that the following fact can be observed: when the edema of the face has disappeared completely, the face becomes more highly colored and pigmented in a very striking manner, and the facies undergoes a complete change. At first I thought that the discoloration at the onset of the illness was due to an acute anemia, and possibly to the hydremia brought about by the retention of water and chlorides. Observations made by MacLeod and myself on the red blood corpuscles and the oxyhemoglobin have shown the same values during the period when the face was pale

as when it was highly colored. It would follow that this initial discoloration was due in greater part to the emptying of the blood vessels of the skin. It seems to me that difference in the color depends less on the amount of blood in the cutaneous vessels than on the presence in the skin of more or less of its usual pigments. In other words, it would seem that at the period of convalescence from this disease, the face does not become flushed, but pigmented. It is well recognized that the edema varies considerably during the course of the illness. At the onset, neither diet nor the use of diuretics prevents its development. A salt-free diet and theobromin cause some variation in its intensity. Thus, even though the treatment is adequately controlled, there may be inexplicable variations in the same patient. No specific laboratory researches on the edematous fluids which we are about to describe have been attempted.

Involvement of the serous membranes. When the edema is very slight and transient, the serous membranes are not involved to an appreciable degree. If the anasarca is well marked, fluid may be demonstrated in the body cavities. Such accumulations of fluid do not seem to me to be very extensive; the pleural transudates were never greater than 1 litre. They were often bilateral, but not necessarily equal on the two sides. The transudate on the one side was always considerably greater than on the other. When a needle was inserted into the pleural cavity, fluid poured out without the use of suction. This does not occur with pleuritic effusions. The cause of this phenomenon is not a greater pressure within the pleural cavity, but a diminished viscosity of the fluid. Furthermore, these fluids in the pleural cavity differ from the inflammatory exudate in that they are more mobile, frequently do not coagulate, and are almost always colorless, being as free from color and as clear as the spinal fluid. Microscopic examination reveals the presence of a large number of epithelial cells, resulting from pleural desquamation, and the presence of red blood cells. Sodium chloride and urea were present in the same proportion as in the blood serum. The pleural exudates are absorbed rapidly and disappear as soon as the subcutaneous edema. Nevertheless, there are two phe-

nomena which seem to me to warrant the statement that they are fairly frequent: (1) Nearly all of the patients that have anasarca with pleural transudates show gastric distension. It has not, however, been definitely determined that the dulness in the flanks is due to the presence of ascites or to edema of the abdominal wall. All autopsies made during the existence of anasarca revealed ascites. In a case which I observed with MacLeod, the ascitic fluid, approximately 3 litres in volume, was frankly chylous, and contained poorly preserved leucocytes, free fat globules, and a pure culture of streptococcus. In a single instance, with enormous edema of the legs, I was able to demonstrate the presence of fluid in both knees. The spinal fluid seemed to me to be under increased pressure in two cases in which I performed lumbar puncture. The urea contained in the spinal fluid was of the same concentration as that in the blood serum. In the case of Mackenzie Wallis, I found 2 cgm. of urea per litre in the blood serum and 4 in the spinal fluid; in one of my cases, 80 in the serum and 56 in the spinal fluid. The duration of the edema has been generally misjudged because of faulty observations. Nearly all observers have regarded it as of extremely short duration. Sir William Osler says: "A large number of men do not show edema except for one or two days—there are only a few examples of general anasarca." I am under the impression that among the patients whom I have examined, general anasarca is fairly frequent, that it exists in at least 25 per cent of the cases, and that the edema lasts a rather long time. If, instead of relying entirely on inspection and on the sign of pitting on compression (which indicate only superficial and marked edema in the area tested), the weight of the patient is used, a much more exact knowledge of the amount of edema and its duration may be had. Nearly all of our patients, when they were given a salt-free diet and theobromin, lost at least 10 kgm. in weight. Thirty per cent lost 15 kgm. or more, and in one instance I observed a loss of 19 kgm. Except in the cases of threatening uremia, which call for a fluid diet, the patients were put on a liberal salt-free diet (beefsteak, potatoes, salt-free bread, preserves). There is, however, no ground for claiming

that emaciation occurred. In several cases, the weight continued to increase in spite of the fluid diet; in others, it remained stationary under the same conditions. In nearly every case, theobromin, if given in sufficiently large doses, caused the weight to diminish. I have given as much as 5 grams a day, but anything in excess of 3 grams is often poorly tolerated.

The decrease in weight may be extremely rapid. Some cases lost 1.5 kgm. per day for more than a week. Others lose their fluid more slowly, at the rate of about 500 grams per day. A fixed minimal weight is obtained in an average of fifteen days. The cure may be permanent or there may subsequently be a rapid increase in the weight which cannot be explained. The resumption of salt-containing food is naturally always accompanied by an increase in the weight amounting to 2 or 3 kgm. in two or three days. I believe, on empirical grounds, that a greater increase in weight and one that lasts longer is the sign of too rapid return of salt in the diet. When it occurs, it becomes necessary to do without salt in the food and to resume it only at the end of ten days.

To summarize, it may be stated that the slightest degree of edema, from the clinical point of view, means the retention of from 6 to 8 litres of fluid, and that under suitable dietetic and therapeutic measures, the complete disappearance of edema requires at least ten to fifteen days.

Urine. Except when hematuria exists, the intensity of the color of the urine corresponds with its volume. If the volume is large, the color is light, and if the urine is scant, it is highly colored, cloudy, and some of its contents are precipitated. The amount varies according to the stage of the disease. At the onset, the quantity is small, but the daily excretion is almost always more than 500 cc. I have never observed absolute anuria. Even in the most serious cases the patients void at least 400 cc. per day. Many cases show scarcely any change in the volume of urine.

During convalescence, the daily quantity of urine does not increase to a marked degree. It reaches a level of 1500 or 1800 cc. Under the influence of theobromin, amounts up to 2, 3,

and even 4, litres have been noted. If water is forced, still more marked diuresis may be obtained. In one of my cases, I brought about a diuresis of as much as 12 litres per day. It is well known that in a normal subject, with theobromin and with a large water intake, analogous amounts of urine may be secreted. This, however, cannot be accomplished in war nephritis except in certain stages of the disease: the period at which the permeability of the kidney, at least the permeability to water, becomes normal. Summarizing the situation, it may be said that at the onset and in the serious cases, for several days, the administration of theobromin, even in large doses, has no influence on the quantity of urine secreted. Giving large amounts of water has no other influence than to increase the edema. There is in the early stages of an acute nephritis an irreducible impermeability of the kidney, which in some instances becomes more marked as the disease progresses.

At the onset, the urine contains an enormous quantity of albumin; heating produces a solid white cloud, and sometimes the urine literally boils solid. I know of no case in which the initial albuminuria was less than 2 grams per litre, and in many cases it was over 20 grams. An albuminuria does not follow the law of regular and progressive diminution, as the other symptoms do. It persists longer than the edema and the other functional disturbances. It does not disappear in all cases, and even when it does, it may reappear without apparent cause, and without impairing in any way the functional efficiency of the kidney. It has no relation to renal function, but it remains a long time as a sign of acute renal disease. The chemical characteristics of the albumin eliminated during acute nephritis have been thoroughly studied by Mackenzie Wallis. The tests show definitely that it is composed of the usual serum albumin and globulin, such as is generally found with inflammatory lesions of the kidney. Other proteins are not present (nucleo-proteins, mucins, Bence Jones proteins, albumoses, peptones). The optic properties of these urines as determined by the polariscope are similar to those of albuminous urines, characteristic of the nephritides. That is, there is an absence of any rotation. The serum albumin is always

in excess, as compared to the serum globulin; the proportion is as 5 or 6 to 1. These figures are the same as have been demonstrated in all the nephritides.

English physicians have paid much attention to casts and have attached great importance to them. J. Rose Bradford, in recording 1455 observations, maintains that casts were found in 794 cases, that they were not demonstrated in 507 cases, and not looked for in 154. He considers their presence so important that he gives no attention in his description to those cases in which the casts were absent. Mackenzie Wallis has found granular casts; a little more frequently, hyalin and epithelial cell casts; rarely, fatty and blood casts. The most important conclusion to be derived from these statistics seems to be the inconstancy of the presence of the casts. In my experience they have been absent in 60 per cent of the cases. This observation robs the symptom of most of its value. On the other hand, I, as well as Mackenzie Wallis, have noticed on centrifuging, the constant presence of a cellular layer. In this layer there are some large cells with round nuclei, either clear or pyknotic. These are epithelial cells from the urinary passages or from the kidney itself. I shall explain their origin in the discussion of the pathological anatomy. The most constant finding is a large number of polynuclear leucocytes. I believe that the presence of a large number of polynuclear leucocytes in the urine has not often been pointed out in the course of acute nephritis. In war nephritis it is constant, at least in the early stages of the disease, and the pathological anatomy will give us the reason therefor. M. Wallis has noted it in several cases of scarlatinal nephritis. Pasteur Vallery-Radot has pointed out to me that similar phenomena have been observed in the acute exacerbations which have occurred in the course of chronic nephritis. Many others have considered hematuria as a common symptom in war nephritis. Certain German monographs characterize it as "hematuric" war nephritis. I believe that the microscopic presence of red blood cells is common, but that macroscopic blood is rare. I found the latter in only 6 per cent of my cases. These include not only the urines which are frankly blood-

colored, but also those usually characterized as "smoky," as well as those having a brownish-red, flocculent precipitate, in which the microscopical or chemical examination revealed the presence of blood. In most instances, hematuria is an initial symptom, and its duration is as long as, or possibly less than, the period of irreducible impermeability of the kidney. In other cases it is secondary, and persists even when the edema has disappeared. In two cases I saw it persist while hypertension, which subsequently became permanent, set in. No relation seems to exist between hematuria and the intensity of the nephritis, nor with its ultimate outcome. M. Wallis noticed a phenomenon to which his special studies have given a certain degree of importance—namely, the diminution in the diastatic activity of the urine, as tested by starch solutions of known strength. By his method, he found that the urine of normal individuals yielded results which he expressed by the figures of 10 to 22.2 units. In all cases of chronic or acute nephritis, the results were much lower, being 0 to 5 units. He makes an exception of the albuminurias of pregnancy, in which the urines maintain a more marked diastatic activity. He has examined about 50 cases of war nephritis, 31 of which had a very much diminished diastatic activity, and 5 showed none at all. The other 19 cases were convalescents, in whom he found figures equivalent to the low normal. In summarizing, two points are to be emphasized: In the first place, the large amount of albumin during the first days of the illness; in the second place, the constant presence at the same time of polynuclear neutrophiles in the centrifuged urine.

Blood pressure. The determination of blood pressure is an indispensable aid in studying the clinical picture of nephritis. I have insisted upon it, especially in the cases of chronic nephritis. There are too few observations regarding it in the acute nephritides and especially in the cases of war nephritis. The only mention of it which I have found in the literature I have been able to obtain is the simple phrase of Osler: "In some cases, blood pressure, which comes on early, and persists, has been noted as out of proportion to the principal urinary symptoms of

the disease; it remains after the albuminuria and hematuria have disappeared." L. Tixier (of Nevers) and I have attempted to average the observations which we have made among our patients. I do not discuss them here, because they are mentioned in the section on edematous nephritis. We have measured blood pressure by the auscultatory method, according to the modification suggested by Tixier. The blood pressure of soldiers in good health, while they are serving in the trenches, is very variable. The average of about 100 readings which we have made under the most varying conditions of military life, is about 125 for the systolic pressure and 75 for the diastolic. It is not necessary to consider these figures as of more than relative importance; moreover, it does not seem possible to demonstrate a normal arterial pressure any closer than 10 mm. Furthermore, it appears, as Pierre Menard has shown, that the arterial pressure among the soldiers varies under different conditions of war activity. Finally, among individuals of the same age, under the same conditions, the subjects being at rest, there are marked variations. In observations made on a division of French infantry in the spring of 1916, I found that the systolic pressures varied between 112 and 155, and the diastolic from 60 to 90. It becomes necessary, in considering the cause of these variations, to take into account the action of alcohol, coffee and tobacco. Consequently it is not possible to accept as pathological any changes except those which are marked and those which are persistent.

In the acute nephritis with edema in troops in the field, the blood pressure may vary as follows: (1) It remains normal or about normal. This is most frequently the case. (2) A slight elevation above the normal. In those cases of acute nephritis complicated by hypertension it may be present at the onset, or it may come on somewhat later in the course of the disease. In about 90 per cent of the cases the blood pressure remained practically normal from the beginning to the end of the nephritis; the systolic readings did not go above 145 and the diastolic above 95. Among healthy soldiers, without a sign of renal disease, such readings are constantly found. In the above cases

the blood pressure did not pass these limits during the period of observation, which, for some of them, was as long as two months. The variations of blood pressure were within normal limits during this period, not exceeding 12 to 15 mm. of mercury. Similar variations are observed during normal health. Neither the clinical changes, such as variations in the intensity of the edema, the accumulation of non-protein nitrogenous constituents in the blood, nor fever, nor changes in diet, brought about any change in the height of blood pressure. The instances of acute nephritis with hypertension are not very numerous, and they constitute less than 10 per cent of all the cases observed. It is necessary to place them in two categories: First, those in which the hypertension comes on with the onset of the disease; and second, those in which the hypertension comes on at a later period. As an example of the former, the following case may be detailed: A soldier had shown a slight swelling of the face and complained only of cough and slight dyspnea. Auscultation revealed a gallop rhythm and an exaggeration of the second sound. The blood pressure was 165 systolic and 115 diastolic. The urine boiled solid. There was a slight edema about the ankles, and he gave a history of having had his face and legs markedly swollen six days before. The serum of the blood contained 0.7 gram urea per litre. The course of the disease was favorable and the patient was returned to active service after a month's convalescence. Five months after the onset of the disease he still had a marked albuminuria, and a blood pressure as on the first observation (that is, 165 systolic, 115 diastolic). This observation shows that certain cases of war nephritis are hypertensive from the beginning, that the hypertension remains for a long time, and that it bears no relation to the intensity of the edema nor to the amount of waste products in the blood. Some hypertensive nephritics improve, as far as their blood pressure is concerned, under the influence of a salt-free diet; that is to say, the blood pressure diminishes under the influence of suitable dietetic and therapeutic procedures, at the same time that the edema disappears. The blood pressure resumes its high level very rapidly, even without the return to a diet containing salt.

In the types with hypertension developing later in the disease, the blood pressure is moderately elevated at the onset and increases slowly or rapidly in direct proportion to the height of the permanent level which it is about to assume. A patient, on the third day of his disease, yielded the following readings: systolic, 150; diastolic, 95. On the fifteenth day prolonged hematuria began, and at this time the blood pressure was found to be considerably raised: systolic, 225; diastolic, 175. The hematuria continued with acute exacerbations during the following weeks, and the blood pressure became somewhat lower: systolic, 205; diastolic, 165, which level was maintained up to the time of the patient's discharge, two months after the onset of the disease. Even at this time there were marked attacks of hematuria. These forms of secondary hypertension have a certain theoretical importance. One is tempted to think that the acute hypertensive nephritis, with its subsequent acute exacerbations, is an important factor in producing a chronic hypertensive nephritis. This explanation is not well adapted to the second type of *acute nephritis*, which will be described subsequently. This is one of the reasons why we believe that this theory should be set aside.

Blood. A complete study of the blood in war nephritis would be of considerable interest. The well-equipped hematologist would certainly find many facts worthy of observation. Without mentioning the bacteriological researches, which will be detailed in the section on the etiology of nephritis, it must be admitted that, in spite of the results obtained up to the present time, the morphological and chemical studies remain most incomplete. Although the patients at the onset of their disease exhibit a striking pallor, often replaced at the time of convalescence by a particularly dark color of the face, and although a very marked edema would indicate a great dilution of the blood, we (McLeod and I) have not been able to discover any marked difference in the red blood cells or in the percentage of hemoglobin. I do not know of any papers published on the leucocyte or the differential count during the progress of the nephritis.

The blood obtained by venapuncture often coagulates very

slowly. I have twice observed the complete absence of any retraction of the blood clot. The blood serum is frequently, though not invariably, opalescent. The delay in coagulation time, the slow formation or absence of retraction of the blood clot, and the opalescence of the blood serum seem to me the most marked characteristics. In two cases of acute edematous nephritis on which I performed the autopsies two hours after death, the peritoneum contained an opalescent fluid. Because of insufficient facilities, I did not make any studies on the concentration of chlorides in the serum, although it is of very great importance to possess data on this point. I did, however, in several instances, determine the urea content of the serum. A few determinations have been published by Mackenzie Wallis. This author used a technique which at present is not employed in France. The principle of the method is based on the conversion of urea into ammonium carbonate by the ferment extracted from the soy bean—the so-called urease. A 10 per cent solution of this ferment in the presence of monobasic potassium phosphate is extremely active. Wallis draws 3 cc. of blood into a test tube containing some crystals of potassium oxalate; he adds 3 cc. of a 0.6 per cent potassium phosphate solution, and 1 cc. of a 10 per cent urease solution. The fermentation is complete in twenty minutes at room temperature. The solution is saturated with potassium carbonate, and distilled into a receiver containing 20 cc. of $N/50$ acid. The remaining acid is titrated with $N/50$ alkali, using alizarin red as an indicator. The difference between the number of cubic centimeters of $N/50$ acid used and the amount of alkali required to bring the solution to neutral, indicates the amount of nitrogen derived from urea in the blood specimen. Multiplying by the coefficient, 0.2, one obtains the amount of urea per litre of blood.

I have described this method, because it may be of interest to other workers. I myself have used the hypobromite method after the precipitation of the proteins of the serum by trichloroacetic acid (method of Moog). This method has been described in the book of Ambard (*Fonctions rénales*). The results which I have obtained are thus comparable with those of various French

workers on the concentration of urea in the blood. From a practical point of view, the figures obtained by the urease method are comparable to ours. At the onset of acute edematous nephritis, the blood urea is always abnormally high. A normal individual on a milk diet, or on a much reduced diet, such as all our cases naturally receive at the onset of the affection, provided the volume of urine is not too much diminished, ought not to have more than 0.50 gram of urea per litre of blood. Higher figures are constantly found in the first days of an acute nephritis; never less than 0.70 or 0.80, and frequently even greater values—up to 3 grams and over. In the mild cases, the blood urea returns promptly to a normal level; in the severe cases, it remains raised over a long period. One of my cases maintained a level of 1.35 grams of urea per litre in his blood for three weeks after the onset of his illness. In this connection it should be remembered that in the acute edematous war nephritis there is rarely any oliguria except at the onset; the daily output of urine nearly always remains normal. Moreover, the concentration of urea in the urine is not very marked, usually varying between 10 and 15 grams per litre. I shall explain the importance of these findings in discussing the pure azotemic nephritis.

In the majority of cases the blood urea returns to normal by the end of the first week; in some it returns so promptly to normal, that unless the blood urea determinations be performed on the first or second day of the disease, no increase will be found. Nevertheless, by means of Ambard's constant, it is possible to demonstrate an impairment of renal function, as far as the excretion of urea is concerned, even after the blood urea has returned to normal. It is known that the value of Ambard's constant is in the neighborhood of 0.07. In all the cases in which it has been determined, it remains higher than 0.10, even after the disappearance of the increased blood urea. However, many of the cases are discharged with a constant of 0.12 or 0.14. In summarizing these findings, it seems to me that it is impossible to have an acute dropsical nephritis without retention of urea during the period of onset and without impairment of function of urea elimination over a long period, the possible duration of

which is not as yet definitely determined. If these facts have escaped those authors who have investigated war nephritis, it is because they have not made their observations early enough, or because they have not made them at all. It is important to recognize this, because the seriousness of the general condition is in direct proportion to the degree of urea retention. Moreover, this often persists over a longer period, especially when it is high at the onset; it frequently disappears with the edema, and does not run in direct proportion with the development of dropsy. It seems to account for certain nervous disturbances (headache, convulsions, etc.), paroxysmal dyspnea and vomiting, which are all observed frequently at the onset of an acute edematous nephritis.

Various inconstant symptoms

Drs. J. H. Clarke and Fontaine have, at my instigation, examined the *eye-grounds* in the cases of acute nephritis and have found them to be normal. J. Rose Bradford has made the same observation. There was only one case of transient amaurosis.

In the severe cases, various *nervous disturbances* have been noted. There may be mutterings or violent delirium, drowsiness and convulsions. Headache is usually, if not always, present at the onset, and its intensity and duration appear to be in direct proportion to the persistence of the azotemia.

The English physicians emphasize the fact that there may be respiratory disturbances, and particularly a dyspnea of such intensity that they designate it as "air hunger." These phenomena seem to be less frequent among my own cases.

In summarizing, it may be said that there is no striking symptom except edema in the cases of acute edematous nephritis. If the edema is slight, it may escape the notice of the patient as well as that of the physician, and it is probable that there is a considerable number of cases of acute edematous nephritis which are not recognized. The other important symptoms are the urinary signs, the changes in the blood pressure and the azo-

temia. Finally, the functional symptoms which might be classed as uremia are very uncommon.

It is justifiable to conclude, therefore, that there are *very mild cases* characterized by transient edema of the face, and possibly a slight edema of the ankles, which frequently go unrecognized because of conditions under which the men live. It is only by accident that these cases are reported and it is impossible to state whether they are of common occurrence or not.

The *mild types* in which the edema lasts only for several days and the albuminuria disappears at the end of two or three weeks, and which are cured, or appear to be cured, in a month or six weeks, seem to be the ones that occur most frequently. It is not possible, however, to be insistent on the above statement, because only a few of the cases were observed in sufficient detail, or followed for more than a very short period, so that neither the duration of the edema, as determined by weight, nor the final outcome of the albuminuria, the blood pressure and the elimination of urea have been satisfactorily determined.

The *severe types* develop in an extremely interesting fashion. The edema in these cases is always very marked during the first days and does not yield to a salt-free diet or to theobromin. In spite of a fluid diet and the administration of medicines in large doses, the weight of these patients not only remains unchanged but often increases. There is, therefore, a period of irreducible dropsy which our theories of the formation of edema do not adequately explain. It is also in these severe cases that the marked and prolonged initial elevations of urea in the blood, entailing uremic symptoms, such as headache and vomiting, are observed. Finally, it is in these instances that the signs of nephritis are found to persist. These are notably albuminuria, recurrent edema, arterial hypertension and impairment of the ability to eliminate urea.

ACUTE PURE AZOTEMIC NEPHRITIS

The clinical picture of acute edematous nephritis, which has just been described, bears a strong resemblance to the classic

nephritis brought about by exposure to cold. If the signs and symptoms of the former are a little more thoroughly understood, it is because the large number of cases has furnished an opportunity for a more minute study. This form of nephritis is readily diagnosed, because the symptoms are very definite, because it is of common occurrence, and because it is the only form which has been described or mentioned by those who have dealt with war nephritis; however, it is not the only form which may be observed. Frequent atypical symptoms, such as those due to meningeal irritation, delirium, convulsions, and at times jaundice and fever, give rise to an albuminuria which, even without the presence of edema, points to some renal involvement in these instances. This supposition is borne out by the presence of a marked increase of the urea in the blood, even though the degree of albuminuria does not always suffice to make a positive diagnosis of nephritis. It is possible, therefore, as Parisot and I have done, to distinguish roughly two forms of war nephritis: first, *nephritis with anasarca*; and second, *azotemic nephritis*.

The latter completely escaped observation until our publications appeared. In the English literature, although it covers many pages on the question of war nephritis, mention is made of nephritis without edema, with albuminuria, frequent hematuria and the infectious symptoms of which we shall speak further on, in only one instance, namely, in the paper written by Hogarth. He did not emphasize the increase of blood urea. This is not to be wondered at, since in general little attention has been paid to this, except in France. Among the German publications to which I have had access, there is but a single communication, that of H. Zondek, which alludes to the retention of nitrogen. This author seems to consider it to be more common and more important than the retention of salt. In France, Merklen, Boidin and Trotain, and R. Mallet have carefully observed and described a certain number of types of these acute azotemias. The subdivision of types has been made because the azotemia brings about many and widely divergent clinical pictures.

The symptoms are extremely deceptive, and lead to diagnoses very foreign to that of nephritis. They have, nevertheless, been classed among the acute renal diseases because of the albuminuria and hematuria, the increase of urea in the blood and the anatomical lesions of the kidneys which accompany them. They have been classified as war nephritis because they appear at the front in abnormally large numbers, and under the same conditions as the edematous form of nephritis already described. Since these cases of acute azotemic nephritis are but poorly understood, are difficult to recognize, and present misleading symptoms, especially at the onset, they should be carefully classified and minutely studied, so that the characteristic features may become well known and that they may be separated from those diseases which they so closely resemble.

Acute azotemic nephritis develops most frequently in the guise of a febrile disease, which possesses no striking clinical characteristics. It is frequently designated as "fever." The temperature rises rapidly, more so than in typhoid fever; the daily variations are frequently much more marked; at times there are remissions, apparently without cause, of one or two days. The pulse is rapid and frequently small. Besides this, there are general malaise, a coated tongue, and obstinate and frequent attacks of vomiting, which as a rule are not observed at the onset of infectious diseases, and finally, persistent and severe headache.

In other cases, a prolonged sore throat, an acute enteritis and generalized ecthyma do not terminate as rapidly as they should, and become complicated with such symptoms as we are about to describe. However, there is no characteristic clinical picture, and wrong diagnoses are frequently made if an examination of the urine is neglected. In the first days of the disease, there is oliguria, most frequently at a level of 700 or 600 cc. of urine per day. One of our patients with nephritis complicated by jaundice died with absolute anuria. The urine at times contains a little or a good deal of blood. On centrifuging, there are only a few, or possibly no, casts, but, on the other hand, a very large number of polymorphonuclear neutrophiles and dif-

ferent sorts of cells may be found. These urines always contain some albumin, and at times a very large amount.

The presence of albumin in the urine is not sufficient to make the diagnosis of acute nephritis when fever exists. Neither the concentration of the urine nor hematuria are pathognomonic. On the other hand, the determination of urea in the blood furnishes a sign by which the diagnosis may be made with probability, if not with certainty. At the onset of the disease, the blood urea is always markedly raised, being as high as 2 grams per litre, and at times it surpasses even this figure. The subsequent level which the blood urea assumes is in direct proportion to the intensity of the disease, and in itself it constitutes an important prognostic factor. If it drops rapidly, the general condition improves; usually its diminution precedes the improvement. On the other hand, if the blood urea increases or is maintained at the initial high level, it is the forerunner of a fatal outcome. Consequently, the increase of the blood urea is a sign of marked significance, the crucial symptom of the disease. It is interesting to note that the patients who have so marked an azotemia have several weeks after its disappearance an increase in the value of Ambard's coefficient. I have even discharged some of these cases before the coefficient had returned to normal. Generally speaking, the change to normal has occurred in about two weeks. There are some fulminating types in which death occurs very soon, but there are also those which are very benign and which are cured in a few days. Again, there are the cases whose course is very much prolonged and whose prognosis is always good. The patients in the last class usually have a certain degree of asthenia for a considerable period. In these cases, the albuminuria, the azotemia and slight elevation of Ambard's coefficient persist after all the other symptoms have vanished, but even these abnormalities have a tendency to disappear after a short period; for all these cases tend to a complete and probably permanent cure. In summing up, it may be said that the clinical picture of acute azotemic nephritis without edema is characterized by marked fever, by albuminuria with or without hematuria, and above all by an increase in the blood

urea. This very simple picture often becomes remarkably complex because of the addition of secondary symptoms. The systematic examination of these patients often reveals acute lesions in other organs. These, although not in any direct anatomical relation to the kidney, are probably brought about by the same etiological factor. Such lesions may dominate the clinical picture, and may not suggest the examination of the urine for albumin or the testing of the blood for its urea content; consequently, the acute nephritis may be entirely overlooked. These cases may be grouped under the name of "Masked Azotemic Nephritis."

MASKED ACUTE AZOTEMIC NEPHRITIS

Nearly all the cases of acute azotemic nephritis should be described under this heading. The usual diagnosis in these instances at the first examination is one of the following: "fever," "gastric fever," or, if there are any signs of organic disease, however slight, they frequently serve to divert attention from the kidney. In some cases, for example, the patient coughs and expectorates a little sputum and has a few sonorous râles in the chest. In other instances, stress has been laid upon these symptoms, because the renal involvement was not noticed, and in the hospital histories a diagnosis of bilateral pulmonary congestion, or bronchial pneumonia, etc., is made, until a more thorough examination reveals the rôle played by the kidney. The most curious as well as the most disturbing mistakes are those induced by the involvement of the nervous system. The considerable headache, the epileptiform seizures, the attacks of delirium and the very marked asthenia during convalescence give rise to a diagnosis of pseudomeningitis, convulsions, delirium and myasthenia, all of which should be described in greater detail. The pseudo-meningitic form is rather frequent. Severe types of this affection, diagnosed as tuberculous meningitis, and having a fatal termination, were pointed out to me by L. Tixier (of Nevers); I myself have observed only mild instances. At the onset, the headache is always marked; in the cases under consideration, it becomes intense, causing the patient to cry out almost continuously. There is stiffness of the neck, and Kernig's sign

is present. However, the temperature is not much above normal. In one of my cases, it did not exceed 38°C. (100.4° F.) during the forty-eight hours. The spinal fluid, in my experience, is invariably normal. The urine always contains albumin, and the blood a moderately increased amount of urea, varying between 0.8 and 1.3 grams per litre. The headache disappears as fast as the azotemia diminishes. The convulsive form may be characterized by only one attack, coming on without apparent cause; in other instances there are repeated convulsive seizures. In the latter circumstance, the disease is always diagnosed as epilepsy. The blood urea remains elevated as long as the convulsions manifest themselves, and this observation goes far to prove that the augmented blood urea was the cause of the convulsions.

The form associated with delirium, as is always the case with uremic delirium, is not diagnosed except by those who have had a special training. A patient exhibiting acute delirium was sent as a psychopathic case to R. Mallet, who was in charge of the psychiatric unit. Mallet recognized the association of these symptoms with azotemia. I had occasion to observe a patient who was discharged from the psychiatric division as a case of confusional delirium who was found to have a considerable azotemia. Boidin and Trotain also note, without making any great point of the observation, that there may be symptoms of tetany, catalepsy, "pseudoperitonitis," and very frequently a type resembling myasthenia gravis. One of their patients was unable to sit up in his bed, and was powerless to move his limbs when the least resistance was made. This condition came on slowly about a week after the onset of fever of undetermined etiology. The patient exhibited a marked degree of albuminuria, and had as much as 5 grams of urea per litre of blood. It is probable that this myasthenia was nothing more than an extreme exaggeration of asthenia, nearly always observed in convalescence from pure azotemic nephritis.

Among the cases of the masked acute azotemic nephritis, there is one form which should be treated separately, because of the large amount of attention which has been devoted to it; this is acute nephritis with jaundice.

ACUTE NEPHRITIS WITH JAUNDICE

We began to observe acute nephritis with jaundice in the autumn of 1915, at the same time that acute nephritis became prevalent. Our first two patients died after a clinical course which only remotely resembled that of icterus gravis. The finding at autopsy of kidney lesions which were evidently of more significance than those of the liver stimulated us to determine the urea in the blood of the inferior vena cava in these cases. The very high level of the blood urea which this chemical examination revealed, and the very marked kidney lesions, led us, as well as J. Parisot and L. Tixier, of Nevers, to lay much stress on the renal involvement and to propose the name of *acute nephritis with jaundice* for this condition. Almost at the same time P. Merklen began an intensive study of this syndrome. Since then, in a very fortunate case, I was able to establish the relationship of this disease with the spirochete commonly known as "*spirochaeta icterohaemorrhagiae*." It became evident that this newly discovered organism was the etiological factor in a great number, if not in all, of the cases of nephritis with jaundice. This conclusion is confirmed by the studies of M. Garnier, who has noticed that in "*spirochaetosis icterohaemorrhagica*" there are urinary signs exactly similar to those which we have noted in nephritis with jaundice.

Now that we have become aware of the true nature of this syndrome, its clinical description loses the interest which has been given to it in all the studies dealing with *spirochaetosis icterohaemorrhagica*. It is above all an infectious disease characterized by fever. The temperature curve in many of my observations is characterized by two or three marked rises in temperature, as is so frequently noted in the infection caused by the Japanese spirillum. The infection often begins five or six days before the jaundice. There is general malaise and pain, with hyperesthesia in the extremities. When jaundice manifests itself it often becomes very marked. It may be accompanied by discoloration of the excreta. Hemorrhages and nervous disturbances are rarely in evidence as they are in the classical icterus

gravis. The blood pressure in our two fatal cases was so low that it could hardly be determined. Death occurred rapidly in these patients. The anuria was due as much to the hypotension as to the renal involvement. In the patients that recovered, the jaundice gradually diminished, and during the very long convalescence there was marked asthenia, to which condition Merklen has justly called attention. In this regard these cases resemble the asthenic form of azotemic nephritis without jaundice described by Boidin and Trotain.

The most prominent symptoms are those related to the kidneys: Frequently, but not always, there is an oliguria, often hematuria, and invariably albuminuria. The bile-pigments are not always present in the urine, even when the jaundice is very marked. Pagniez and Scheikevitch believe that this abnormality occurs because of the diminished permeability of the kidney.

This fact seems to me evidently substantiated by the increased non-protein nitrogen in the blood. A patient whose data Lemierre is about to publish showed a gram of urea per litre of blood three days before the jaundice appeared. Hence it is apparent that considerable degrees of azotemia may be present before the jaundice is manifest. In one of my cases it was more than 6 grams per litre at the time of death. In those patients that recover, the blood urea falls to a point at which it is equal to, or even less than, normal (0.3 gram to 0.5 gram). However, even under these circumstances, the excretion of urea is interfered with, as is proved by Ambard's coefficient, which, for several days, and sometimes even weeks, remains equal to or above 0.1. As Merklen has noted, the excretion of urinary nitrogen is very low during the early stages of the disease, and it may become enormous at the time that polyuria sets in.

Marklen believes that the azotemia is present in every case of infectious jaundice, and that if it is not found constantly it is due to the fact that the determinations are not made early enough. If the blood of these icteric cases be examined, as Lemierre has done in his own patients, before jaundice appears, an increase in non-protein nitrogen is always found. In the mild cases this disappears very rapidly and consequently a

delayed examination may fail to demonstrate it. It is possible, even probable, that similar conditions prevail in the cases of infectious jaundice of the catarrhal type, in the severe primary jaundice, and in the cases of secondary infectious jaundice, provided they have some involvement of the kidneys. But it must be admitted that there are cases of jaundice characterized by the signs of an infection in which the organic lesions are limited to the liver and do not affect the kidney. It is in these instances that the azotemia and abnormal Ambard's coefficient are absent.

Consequently it may be considered proved that this syndrome of jaundice should be classified with war nephritis when there is evident involvement of the kidney. Further on we will speak of the facts which have been developed in the study of these two subjects, the jaundice and the nephritis, when considered in conjunction with one another.

SIGNIFICANCE OF THE AZOTEMIA IN WAR NEPHRITIS

In acute azotemic nephritis, which we are at present considering, all symptoms, even the most usual ones, such as albuminuria and fever, may be entirely lacking. The essential characteristic of this form of nephritis is, therefore, *hyperazotemia*.

These cases of acute azotemic nephritis without symptoms are in marked contrast to the cases of acute edematous nephritis. The latter are much more common, more generally recognized, and have very striking symptoms.

In a general way, the picture of acute azotemic nephritis is more alarming during the first few days than that of the edematous nephritis. On the other hand its course is very much shorter. Azotemic nephritis develops very rapidly and constitutes an immediate menace. However, if the patient survives the first few days, he recovers completely without complications. This, at least, was the case in those individuals that we were able to observe.

In nephritis with edema the onset is less violent, but much more prolonged. The mortality is negligible. There is a rapid and

favorable therapeutic result from diet and other appropriate measures. However, the albuminuria is much more marked at the onset, lasts for a long time, and often persists indefinitely. The edema may reappear during the first weeks if there is the slightest error in treatment. The patients who are entirely cured at the end of two or three months of careful supervision are exceptional.

In spite of this apparently absolute distinction between these two types, it is frequently impossible to differentiate between them. Acute azotemic nephritis may occur without the association of edema. On the other hand, cases of acute edematous nephritis without retention of urea are not observed. The blood urea during the first three days of an acute nephritis with anasarca is always higher than normal. This increased blood urea results in a clinical picture characterized by marked general depression, nervous disturbances, dyspnea, and vomiting.

If due allowance is made for the constant presence of azotemia and for the part it plays in bringing about the functional disturbances in nephritis with edema, the inevitable conclusion must be reached that the basis for the clinical picture of all war nephritis is to be found in the increase in the non-protein nitrogen in the blood.

It is advisable to discuss the common, as well as the distinctive, characteristics of these two chief forms of war nephritis that we have described. Inasmuch as their etiology is as yet uncertain, we may discuss the following question at this time: Is it possible to demonstrate a single cause for these two types of nephritis?

Since the azotemia is the connecting link between them, it is advisable to have a thorough understanding of its pathological significance. Widaland his pupils have studied this satisfactorily in chronic nephritis. The war, however, has resulted in so great a number of cases of acute azotemia that it is necessary for the first time to consider the importance and significance of this symptom in acute nephritis. In those cases which we have described we believe that the azotemia is indicative of renal insufficiency. It is a question whether this condition can always

be ascribed to renal insufficiency or whether there are instances in which it may occur without any renal lesion.

It appears that there is a certain lack of unanimity of opinion in this regard. Thus Gautruche voices his ideas in these words,

It is known in a general way that it is necessary to distinguish transitory azotemias, that is, a marked temporary retention of urea occurring in the absence of Bright's disease, from the permanent increase in blood urea characteristic of nephritic uremia. In the former condition there is a large margin of safety and it has relatively little significance in the causation of clinical symptoms. Mosny and Javal have recently emphasized this point. They report similar periods of acute retention followed by a complete cure in cases of acute nephritis (Widal), cholera (Froin and Marie), and pregnancy (André Weil and Wilhelm). We ourselves have observed several instances in cases of scarlet fever complicated by nephritis in children.

This confusion exists because of the difficulty in distinguishing between the *prognostic* and the *diagnostic* significance of azotemia. Widal has shown that in chronic nephritis there is a fatal outcome when the azotemia attains a certain level. "The organism cannot tolerate a concentration higher than 4 grams of urea per litre of blood for any length of time." If the blood urea ranges from 0.50 to 1 gram per litre, the prognosis should be guarded; from 1 to 2 grams, death usually occurs within two years; above 2 grams, there is a fatal outcome within less than a year; and with 5 grams or more the end is imminent. These observations are correct if they are applied only to the azotemia which occurs in the course of a chronic nephritis. Such an azotemia increases steadily though slowly during the course of the disease.

This "prognostic table" is not always correct. Especially in the instances of acute nephritis, which Gautruche mentions, it may be at fault. Widal has pointed this out very distinctly in his observations on the prognosis of azotemic nephritis. In chronic nephritis, as mentioned above, the prognosis may be measured definitely according to the standards given, but in spite of this it must be borne in mind that the azotemia in acute nephritis results in very definite symptoms. In acute nephritis

a marked azotemia may develop. The urea may be higher than 1 gram per litre of blood. This indicates that in such a patient the renal function has been correspondingly diminished, so that, according to Ambard, 90 per cent of its efficiency may have been lost. When this occurs there has been a transient renal insufficiency. The clinical conception of transitory acute nephritis has been accepted for so long a time that we are justified in admitting the existence of this condition.

Consequently, if the azotemia has a considerable prognostic value it has a still greater diagnostic one. It indicates either a permanent or a transient renal insufficiency, the cause of which must necessarily be determined. It is essential to recognize the fact that there may be a transient azotemia because of insufficient excretion of water, i.e., an *oliguric azotemia*. It is to the credit of Ambard to have demonstrated both the existence and the cause of this condition. At the present time it is well known that a normal human being is not able to concentrate urea in the urine above a certain level. This concentration, which Ambard has called the *maximal concentration* for urea, is 55 grams per litre of urine. Consequently, an oliguric patient whose volume of urine is 100 cubic centimeters can under no circumstances eliminate more than 5.5 grams of urea per day. If, during this period, he metabolizes enough protein to produce 15.5 grams of urea per day, the usual amount eliminated by the French soldier, he will be forced to retain 10 grams. Since it is known that the retained urea accumulates in the blood, it is evident that, under these circumstances, an azotemia results, even though there is no impairment of renal function. An example of this form of oliguric azotemia is the *choleraic diarrhoea associated with oliguria*. Froin and P. L. Marie reported a case in 1911 in which the blood urea rose as high as 4 grams per litre. Similar findings have recently been recorded (as high as 6 grams per litre) by Lesieur; I demonstrated a blood urea of 2 grams in a patient with choleraic diarrhoea and oliguria as the result of mushroom poisoning. This case showed no important renal lesions at autopsy.

It is possible to estimate the true state of affairs in regard to

these azotemias if, according to Ambard's suggestion, the patient is voiding a urine of *maximal concentration* at the time that the blood is examined. I should suggest that this additional differential diagnostic point be also taken into account: an individual with a sudden rise in blood urea as the result of an oliguria will exhibit a return of his blood urea to its normal level with the onset of polyuria, and furthermore, when the blood urea is again normal, Ambard's coefficient is not raised. On the other hand, in the cases of acute azotemic nephritis, the blood urea assumes normal values sooner than Ambard's coefficient. In these cases the blood urea is less than 0.5 grams per litre for a long time, although the coefficient is maintained at 0.12 or 0.14, values which are evidently above normal.

It may be that there are cases in which both factors play a part, that is, cases in which azotemia appears to be due both to oliguria and to renal insufficiency. In the first two instances of "nephritis with jaundice" that I observed, there was a very high blood urea associated with an oliguria. In the fatal case with six grams of urea per litre of blood, there was marked oliguria for several days. Possibly this oliguria may be attributable to the very low blood pressure present in this type of the disease, and the azotemia in turn would appear to be exclusively due to the oliguria. At autopsy I found important acute renal involvement, such as an interstitial polynuclear infiltration. Furthermore, similar cases subsequently observed had a very marked azotemia, while their daily urinary output was of normal quantity. In these instances, therefore, the azotemia seemed to me to be a sign of renal insufficiency.

This interpretation was later discussed by Merklen. In his earlier publications concerning this syndrome, which both of us have observed and which I have called *acute nephritis with jaundice*, he acknowledged the simultaneous involvement of liver and kidney. He called this condition *acute hepato-nephritis*, and considered the azotemia a sign of renal involvement. At a later date he appears to have modified this opinion. He observed that in cases of infectious jaundice the non-protein nitrogen of the blood was almost invariably increased, and independently

formulated the opinion that the liver played a part in bringing this about.

A priori the idea that an increase of urea may occur in the blood as the result of disturbed liver function is somewhat paradoxical. It is not possible to believe that urea should accumulate in the blood in response to a chemotactic influence exerted by the bile pigments, or, to put it tersely, that the cholemia causes the azotemia. This is proved by the large number of cases of jaundice in which no increase of the blood urea is noted. Consequently, if it is desired to attribute a part of this disease-picture to the liver, it becomes necessary to recognize the fact that the hyperazotemia of infectious jaundice is due to hepatic insufficiency. This conception meets with some difficulty, since we usually presume that the reverse is true, believing that a hepatic insufficiency is associated with a diminution of blood urea.

Without going into greater detail, we may assume that nephritis with jaundice is the result of a septicemia which at times involves the liver and at times the kidney. Thus, either renal or hepatic symptoms may be in evidence. It must be remembered that in certain cases there are extra-renal and extra-hepatic symptoms pointing to an involvement of the circulatory organs and the nervous system, and that distinct pathological lesions may be found in all these tissues. This hypothesis would receive additional proof if, in the future, it could be established that "nephritis with jaundice," "hepato-nephritis," and possibly many of the cases of the common type of infectious jaundice, were all caused by the Japanese spirochete.

PROGNOSIS IN WAR NEPHRITIS

In spite of all the observations made upon pathological lesions in the kidney, all the facts which have been acquired during the past few years by a study of the pathological physiology of the kidney, and the progress made in interpreting the symptoms of renal insufficiency, many physicians know nephritis by no other sign than albuminuria. A great number of clinicians are content to formulate their prognosis according to the kind and

amount of urinary albumin and the length of time it has been present. This accounts for the fact that in the papers previously published, there is frequently a lack of understanding concerning the course which the disease may be expected to follow. Every observer has noted that the albuminuria very often disappears with great rapidity. Consequently, many believe that these cases are as mild as they are brief.

The question of prognosis in acute nephritis must be studied from two points of view. In the first place it is necessary to think of the immediate danger and the chances of recovery; and in the second place, if the immediate danger be overcome, to consider the return of renal function to normal. Will the patient die, or will he live? If he does not die will he be in good health, or will he remain an invalid with an impaired kidney?

The *immediate prognosis*, that is, the *vital prognosis*, varies in the cases of pure azotemic and of edematous nephritis. The former is much more dangerous than the latter. The degree of azotemia does not seem to me a good sign on which to base prognosis; patients with high blood urea often recover. The persistence of the azotemia seems to me to be more ominous. In a word, a marked increase in the non-protein nitrogen content of the blood, if it be of short duration, is compatible with recovery; on the other hand, if the blood urea be high and persistent, and especially if it exhibit a tendency to increase slowly, there is usually a fatal issue. In two cases of nephritis with jaundice, very marked oliguria and hypotension were observed. It is possible that these two signs may, in the future, be demonstrated as significant of a bad prognosis.

The *immediate prognosis* in *nephritis with edema* seems to me to be much less serious. I have not lost a single case of all those that I have treated. Poor housing or bad care render the prognosis more serious. If a nephritic in spite of his disease, remains in the trenches and spends ten or more days without rest, shelter, diet, or medical supervision his condition may obviously become greatly aggravated. It is therefore wise to insist on the importance of rest and nursing, and to institute certain therapeutic measures. At the onset the nephritic voids very little

urine and retains much that he should excrete. It is therefore necessary to reduce his solid food to a minimum and to force fluids, so that the amount of urine secreted shall be as high as possible. This mode of therapy is absolutely indicated if the power of concentration is very much diminished. Therefore, during the first two or three days, the diet should be largely fluid and very abundant. This procedure may be used during the first period of the disease, a period which I have called the "irreducible phase," during which the edema remains stationary or increases, uninfluenced by any treatment. It must be understood that the fluid is to be forced only during this stage of the disease. The worst which can happen is that the edema may increase a little during this period, but the duration of the "irreducible phase" is never prolonged nor the general condition made worse. When the weight of the patient begins to diminish it becomes necessary to increase the nourishment. Bearing in mind that an azotemia exists, it is wise to order a diet composed exclusively of milk. Finally, when the azotemia has disappeared, a salt-free regimen, including many articles of diet besides milk, may be advised. Under these conditions there is no chance that the edema will reappear. I have already mentioned the part which theobromin plays in the treatment of these cases.

The *ultimate prognosis*, that is, the prognosis of possible chronic invalidism, is to be made with much more reserve than the immediate prognosis. The reason for this is to be found in war conditions. A medical patient who has a disease of some duration is successively observed by a half-dozen doctors who are not in touch with each other in spite of the rules which have been laid down. A case of acute nephritis is sent to the rear as soon as it is possible to transport it; the physician who has charge of him in the first place is not the one that takes care of him during his convalescence, and the latter, in turn, has no record of the final disposition of the patient. It is on this account that we have no information at the present time relative to the ultimate prognosis of war nephritis. In the foreign literature I have been able to find only very fragmentary observations. These have, for the most part, been based on the persistence or the disappear-

ance of albumin. The writings of Sir William Osler are the one exception in this regard. He lays stress on the prognostic significance of hypertension. It would seem that from now on the prognosis should be based upon a study of renal function as determined by modern methods.

Acute nephritis with azotemia which is not immediately fatal ends in a very rapid recovery and these cases are, moreover, completely cured, so far as a normal blood urea and normal Ambard's coefficient may be conclusive. The reports which I have from former patients convince me that this cure is definite and permanent. It is necessary to emphasize the fact that these cases of acute azotemic war nephritis recover quickly and completely, because this is not true of all the acute cases with azotemia. I was particularly interested in two instances of azotemic nephritis following anti-typhoid vaccination. At the end of six weeks these patients still had evidence of a slight intermittent albuminuria, and, what is particularly important, an Ambard's coefficient fixed at a level of 0.13.

The ultimate prognosis of acute edematous nephritis is vastly different. This form of the disease involves the kidney more seriously and more permanently. Lafosse has called my attention to the fact that some of my old patients whom he has traced were able to resume their military work at the front. On the other hand, M. René Marie has, in the course of his duties as divisional chief, been called upon to examine some of the old cases of edematous nephritis, and he has reported to me that it was necessary to have many of these individuals sent into the auxiliary service. The question, therefore, is both medical and military. This is true because the cases of acute nephritis with edema are followed by sequelae that are very likely to impair the efficiency of the man as a soldier, possibly making him a permanent invalid. This disability may be so great that the soldier becomes dependent upon the care of others and deserves a pension as much as those with other injuries contracted during military service.

The sequelae of this form of nephritis are as follows:

1. *Persistent albuminuria.* This is frequently very irregular, and may be present in large quantities or, which is very frequently the case, as intermittent traces. No information as to the degree of renal involvement can be deduced from these albuminurias. The whole question regarding them, including that of their significance, is far from clear.

2. *Tendency to edema.* This is not very frequent, but some patients maintain an appreciable degree of edema, which continues for several months after the onset of the illness. In others it has a tendency to reappear several weeks after the apparent cure. This tendency towards edema is recognized much more readily if the patients are weighed every day, especially at the time that the salt in the diet is resumed. It is frequently observed that the weight increases very markedly at this time. In order to be thoroughly oriented in such cases it is necessary to perform the chloride tests devised by M. Widal, which make it possible to estimate the permeability of the kidney to sodium chloride.

3. *Diminution of the ability to excrete urea.* In many cases the impairment of urea excretion persists for some time. The hyperazotemia disappears fairly rapidly. In those cases in which the azotemia is most marked, Ambard's coefficient has a tendency to remain high for a longer period.

4. *Arterial hypertension.* This complication is a rare one, but when present it has a tendency to persist for a very long period. I recall a case which, five months after the initial symptoms of hypertensive nephritis, had the same blood pressure as at the onset. The blood pressure of all types of hypertensive nephritis apparently remains at the same height for an indefinite period. In short, although scarcely one case of nephritis out of ten exhibits hypertension, when the hypertension does occur it has a tendency to remain indefinitely.

The ultimate prognosis of acute edematous nephritis cannot be formulated except by the physicians who have the final disposition of the patients, either ordering them back to active duty or to the auxiliary service, or recommending their discharge. An intelligent prognosis in these cases can be arrived at

only if the functional renal studies and the blood pressure determinations are obtained. It is only in the years to come that we shall know the significance of diminished ability to excrete urea, of a permanent hypertension, or of a persistent albuminuria in these cases of nephritis. What Sir William Osler has said is probably correct: "We shall have a less rosy view of war nephritis in the future."

PATHOLOGICAL ANATOMY

The pathological anatomy of war nephritis rests on very slight evidence, since the disease is a relatively benign one. Andrewes, who has made a study of all the cases brought together by the Medical Research Committee, was able to obtain material of but six cases in February, 1916. Sir J. Rose Bradford has made only three autopsies. I have been able to examine the sections of no more than six cases. One of these was sent me by Ph. Pagniez, and two others were kindly submitted to me by my colleagues, MacLeod and Clarke.

Other reports have been published, but exception may be taken to certain of them because sufficient allowance was not made for post-mortem changes, which may have a very great bearing on the gross, as well as the histological, picture of the kidney.

Granting this, it has been found, as in previous cases, that the kidney may have a normal gross, as well as microscopic appearance, even when there is clinical evidence of a very marked acute edematous nephritis. It has been noted in acute nephritis that at the time of onset the kidneys reveal a histological lesion which has been rarely demonstrated, namely, an interstitial exudate of polynuclear cells. At a more advanced stage, as Andrewes has shown, the glomeruli and the tubules are involved in a manner similar to that generally observed in sub-acute nephritis.

The kidneys are nearly always larger than normal. Sometimes they are reddish-brown or have the red color characteristic of congestion, and the stellate arrangement of veins beneath the

capsules is very evident. In other instances, as in the case of Osler, they may be absolutely white, a milky white without even a trace of red color in the cortex, and without evident veins beneath the capsule. In the early stages the kidneys are frequently mottled, and sometimes, as I noted in one case, grayish-yellow nodules about the size of a millet-seed, resembling a miliary tubercle, may be found. Under the microscope the surprising observation is occasionally made that there is no lesion whatsoever. Andrewes performed an autopsy upon a soldier who was found dead by the wayside. This man had evident anasarca, and his bladder contained a urine in which there were albumin, blood and casts. The diagnosis of acute nephritis seemed justified. Microscopically, there were no lesions either in the glomeruli, the tubules, or the interstitial tissue. Another English soldier, on whom I performed the autopsy, presented degenerative lesions in the liver and the myocardium and slight inflammatory signs in the lungs; in the kidney, however, no significant changes were found. This patient died on the thirteenth day of what was undoubtedly an acute edematous nephritis.

In those cases in which death occurred during the first stages of the disease there are only interstitial lesions in the kidneys. The glomeruli appear to be intact. The tubules are usually very much dilated; they may be broken up here and there as the result of the breaking through of interstitial inflammatory products in their lumina; however, with this exception, no lesions in them are evident. In the autopsies made on fresh material in which there were no post-mortem changes, I have been struck with the normal appearance of the tubular epithelium; in contradistinction to this, the interstitial changes, comprising congestion, edema, and exudation, are very prominent. The capillaries are so distended that they will admit twenty to thirty red blood cells abreast. The tubes and the glomeruli are separated from each other not only by the distended vessels, but also by an interstitial edema, which in section has the appearance of layers of fine, albuminous, more or less confluent, granules. Finally, of especial importance, is the occurrence of

foci of exudate so arranged that they have the appearance of miliary nodules. It has become conventional to describe an exudative type of acute nephritis. This type is characterized by the accumulation of cells composed almost exclusively of lymphocytes about the glomeruli. Therefore this form of nephritis has been described as the lymphomatous type. The exudate of war nephritis consists in greater part of polynuclear cells which have become more or less changed, and, to a less extent, of macrophages, plasma cells, and also of large cells with pyknotic nuclei and a homogeneous markedly acidophile protoplasm, which are the remnants of the degenerated cells from the walls of the tubules. Among these cells are found some minute filaments of fibrin and a small amount of edematous exudate. These small infectious nodules hardly ever involve the glomeruli. On the other hand, they have a tendency to invade the walls of the neighboring tubules and to penetrate into their lumina. As a result of this process, there is a large number of tubules which, although their walls are intact, are stuffed with leucocytes similar to those which are found in large numbers in the urine. This inflammatory exudate is not diffusely distributed, but confines itself to certain localities and forms distinct foci. Sometimes, however, it parallels the tubules in the interstitial tissue and assumes an elongated shape. Finally, there are instances in which these inflammatory nodules become large enough to be visible to the naked eye, as in the cases which I have described above, when they simulate small tubercles.

Other lesions which are somewhat less characteristic may be observed at a later stage of the illness. They are described by Andrewes, according to his findings in four cases in which death occurred between the fourth and the twelfth week of the disease. He demonstrates nephritic lesions involving the glomeruli, the tubular epithelium, and the interstitial tissue.

1. *The glomerular lesions.* There is a proliferation of epithelium in the capsule of Bowman which forms a cellular crescent that gradually obliterates the glomerular tuft.

2. *The lesions in the tubules.* These are characterized by degeneration of the epithelial cells. (This description possibly

does not discriminate sufficiently between the post-mortem and the true changes in these cells).

3. *The lesions in the interstitial tissues.* These are similar to those which have already been described as characteristic of the early stages. Thus far sclerosis has not been noted. However, it must be recognized that this may be encountered when cases of long standing are autopsied.

All of the kidneys which I have examined microscopically have exhibited lesions which I believe antedated the terminal illness. These occurred as fibrous glomeruli or small areas of interstitial sclerosis, and were distinctly isolated changes. Andrewes also demonstrated marked lesions of chronic nephritis in one of his cases. It is not necessary to attach much importance to such anatomical changes provided that they are the remains of a chronic process. It is the rule to find such changes in the kidneys of a man of military age, regardless of the cause of death. These legacies of previous renal involvement may, if they are very marked, have a considerable bearing on the disease which we are considering at present. In the statistics of J. Rose Bradford there are but three fatal cases. The first of these was a patient who had been the subject of a chronic nephritis; the second had a congenital, bilateral renal anomaly, and the third had but one kidney.

When a pathologist performs an autopsy on a case of acute nephritis, he naturally lays stress upon his findings in the kidneys and does not investigate the condition of the other organs with equal care. This is evidently the case in the anatomical descriptions of war nephritis which we have at hand at the present time. Unfortunately, the true state of affairs is not usually appreciated, for the changes occurring in war nephritis are not limited to the kidneys, but are also found in the liver, the lung, the myocardium, and doubtlessly other organs.

From the clinical point of view, it is always the liver which, next to the kidney, attracts attention. In one case I demonstrated an incipient cirrhosis. In this subject, as in all the others, I found the changes characteristic of an infectious hepatitis; on inspection, the liver was large and heavy and showed

yellow mottled areas beneath its capsule; microscopically, there were irregular areas of capillary injection alternating with others in which there was marked fatty infiltration or cellular degeneration. There were scattered areas in which inflammatory nodules were present. These consisted of a collection of polynuclear cells, macrophages, and of plasma cells. However, such nodules were small, extremely sparse, and never attained the density or the importance which they assumed in the kidney.

It is usual to find a marked degree of broncho-pneumonia in all of these cases, a condition which exists because the lung is nearly always involved when there is a general infection. These lesions are naturally always outspoken. They usually consist of large or small areas of hemorrhagic broncho-pneumonia in the posterior portion of the lung. They are surrounded by an area of splenization which may be sharply demarcated or may become confluent with the broncho-pneumonic tissue. In the microscopic sections hemorrhages, inflammatory exudate and edema are seen in all the alveoli.

It is advisable to lay special stress on the lesions which occur in the heart muscle. They demand emphasis because they explain the symptoms of myocardial insufficiency which form so important a part of the clinical picture in the first days of the disease. These lesions are scattered through the tissue as small isolated foci. The muscle fibres lose their striation, become moniliform, and often undergo evident hyaline degeneration. Sometimes there are very small focal lesions similar to those, but smaller than the inflammatory nodules, previously noted in the kidneys. These findings adequately explain the dilatation of both ventricles that is frequently evident at autopsy.

As a result of these studies the following points should be emphasized:

1. The kidney is not the only organ which undergoes pathological changes in war nephritis; there are inflammatory and degenerative foci in other tissues which have no direct organic connection with the kidneys.

2. At a certain stage of the disease there is an acute interstitial lesion in the kidney, consisting of edema and of an exu-

date of polynuclear cells; this change is pathognomonic. Andrews claims that he has found a similar lesion in scarlet fever; he must acknowledge, however, that the renal infiltration in the latter disease is composed of lymphocytes and not of polynuclear cells. The interstitial exudate composed of polynuclear cells has been found by Tapret and Roger in certain cases of typhoid fever complicated by nephritis. Gallois has observed it in various forms of acute infectious nephritis. It should be borne in mind that in these cases there was an evident tendency to suppuration.

These two very important anatomical characteristics found in the edematous, as well as the azotemic, type of nephritis, and even in the nephritis with jaundice, go very far to establish a certain relationship between them.

It is evident that pathological anatomy which thus far has served as a means of classification for the nephritides is not a criterion by which the clinical types of renal disease may be grouped. The conception so closely adhered to in former years was full of promise. Later developments have cast some doubt upon it, and this skepticism is justified to some extent. When all the facts are taken into consideration, however, the discrepancy is not as great as it would seem to be at first sight. The similarity which we have noted in the pathological-anatomical lesions among the different types of war nephritis forces a very important question on our attention: Is there a single etiological factor which is responsible for all the types of war nephritis observed hitherto?

ETIOLOGY

It is essential to lay stress on the fact that war nephritis is not synonymous with simple transitory albuminuria appearing without cause or during the course of an infectious disease. The nephritic albuminuria occurs without evident cause and apparently is not secondary to any of the common diseases. It is much more frequent than the acute nephritis brought on by cold and exposure which is so often seen in times of peace. There are many observers, at least in France, who still believe that it is

not necessary to attribute these peculiar pathological manifestations to war conditions. They believe that the findings are exactly similar to those which are met with during peace. I would refer to the percentage tables cited at the beginning of this article in order to indicate the importance which war nephritis has assumed in the present conflict.

In recent wars, typhoid fever and dysentery have been the common diseases. Acute nephritis has played but a small rôle. In the war of 1870, the Chino-Japanese, Spanish-American, and Russo-Japanese wars, the medical records lay no stress on this malady. During the Boer war the English, who have suffered so much with nephritis in the present campaigns, appear to have had little or none of it. There were but six cases in the Base Hospital at Deelfontein, and three at the Portland Hospital. L. Brown, who followed the Boer war closely from the medical point of view, did not meet with a single case.

On the other hand, the observations made during the Civil War in the United States tell a somewhat different story. Nephritis was very rare at the beginning of the war in 1861, but gradually increased so that there was a mortality of 1.6 per thousand by the middle of July, 1862; from that time on it diminished progressively up to the end of the war. The following table gives the number of cases and the death rate from nephritis in the armies of the Northern States:

	NUMBER OF TROOPS	NUMBER OF CASES OF NEPHRITIS	NUMBER OF DEATHS
May-June, 1861.....	42,500	27	—
July, 1861 to June, 1861.....	279,000	1,790	45
July, 1862 to June, 1863.....	614,000	6,603	148
July, 1863 to June, 1864.....	619,700	2,677	81
July, 1864 to June, 1865.....	574,000	2,744	77
July, 1865 to June, 1866.....	161,800	346	9
		44,187	360

Analyzing these statistics more closely, it becomes evident that the percentage of nephritics in proportion to the number of troops engaged increased more rapidly and assumed greater

proportions in the Central Army than in the others. This is particularly true in the period from July, 1862 to March, 1863. It was at this time that the army was conducting its campaign in a manner very like that which we are employing at the present time. A sudden offensive on the part of the Confederates was checked, and a long period of trench warfare followed.

In the present war it is in the British Army especially that this disease has assumed alarming proportions. The official statistics obtained at the beginning of the war have been published, and it is permissible to quote them here. Scarcely any cases were observed up to February, 1915. There were 72 cases in February, 138 in March, 211 in May, and 326 in June. By the end of June, 1062 cases had been reported and the number was constantly increasing. This increase was more rapid than the number of men enlisted warranted. Although unable to give any definite figures, I believe I am justified in stating that the number of cases observed in the British Army is far greater than that in ours. Up to the present writing it has been impossible for me to form a concrete idea concerning the prevalence of nephritis in the Italian or Russian Army.

There seems to have been a considerable number of cases in the Expeditionary Force at the Dardanelles. Thus, S. N. MacBean Ross, in speaking of the troops under his personal care, says that, although it was not possible to designate the prevalence of the condition as an epidemic, yet the cases of acute nephritis were extremely common in his battalion. The prisoners interned in Germany under the lamentable hygienic conditions of which we are well aware, appear to have suffered very much from renal disease. In the report of Breton, which was made from the hospital at Münster, covering the period from the 7th of December, 1914, to the 1st of June, 1915, the following figures are found: Among 158 sick prisoners under treatment, there were four cases of simple albuminuria and three patients suffering with nephritis, one of these with a fatal uraemia; this makes a proportion of about 2 per cent. In the same connection this author makes the interesting observation that a large number of

prisoners confined under his care evidenced a cachectic edema without albuminuria.²

The number of enemy publications on the subject of nephritis indicates that it is equally prevalent in the Austro-German army. It would seem that they suffer more in this regard than we do, and about as much as the English. It may be noted from the discussion which took place on this subject at a meeting of the Vienna Medical Society in 1915 that the marked increase of war nephritis among their troops occurred at about the same time as among the soldiers of our Allies. It is very striking that the Hindoo forces of the English have been almost absolutely immune from nephritis.

In the French army, war nephritis, although it is common enough, is much less frequent than it is in the other armies. It was also much later in manifesting itself. According to Langdon Brown, at the time when it was first called attention to among the English, there were only cases of malingering (mixture of egg-white with urine and subcutaneous injection of water) among the French. I, for my part, have never met with this type of malingering, and I have never heard it mentioned as being used in the present war. I know of no such official report concerning war nephritis in our army. I believe that the first cases of nephritis were diagnosed as isolated occurrences during the summer of 1915. When Parisot and I published our first report in November, 1915, we had observed hardly twenty instances. Toward the end of autumn these cases became very

² Dr. Malergue of Ussel, who was physician of a prison camp during ten months of captivity, gave me the following very curious information concerning this special form of edema. This edema is moderate in degree, soft, and limited to the feet, not rising any higher than the malleoli. There is no albuminuria, but frequently a bradycardia is present. (In one case, 32 beats to the minute.) Malergue believes that this edema is without doubt due to the inanition and to the kind of food which is offered to prisoners. The diet is entirely liquid, consisting of about two liters of very thin soup. The Russian prisoners were particularly subject to this symptom. These diets have been deemed adequate by the learned food specialists of Germany. It sufficed to give these unfortunates a "double ration" in order to obtain a disappearance of the bradycardia in three or four days. The edema, however, persisted for several months.

much more numerous, and this was especially true during the spring and summer of 1916.

The inspection of the lists of individuals ill with nephritis emphasizes certain facts. The men who do the actual fighting, and especially infantry, are more often affected than the troops not in the line. Among my present cases there have been no men of the latter class, with the exception of two hospital nurses; stress has often been laid upon the susceptibility of hospital attendants to war nephritis. I performed an autopsy upon a chauffeur of the English Sanitary Corps, who died of a severe nephritis. Among the combatants the sappers are most frequently affected, and they comprise 7.5 per cent of my cases. I have often met with cases of nephritis among the men engaged in the construction of earthworks.

It is important to recognize the fact that officers are almost absolutely immune from war nephritis. I have never seen an officer affected by it. This fact is well brought out in the official English statistics, in which it appears that not a single officer, with the exception of one chaplain, suffered with this disease. Finally, another factor to be taken into consideration is the length of time which a soldier has spent at the front. Most of the patients have been in the front line since the onset of hostilities, or at least for a period of one year, without having been sent home because of illness or of wounds. At least 80 per cent of our patients fall into this class; and yet in the infantry at least, there are only 20 per cent who have remained at the front this long. This fact is in strict accord with the following observation: Two English divisions were quartered in adjoining sectors and under absolutely similar conditions during the months of May, June and July, 1915. The first of these had arrived in France at the beginning of hostilities and in it there occurred 77 cases of acute nephritis; the second took up its duties on French soil in May, and in this division only 2 instances of war nephritis occurred. These reports agreed with those of the evolution of the "epidemic" which occurred in the American Civil War. The course of events may be summarized in the statement that during the first months of fighting the disease

did not occur, but that from the sixth month on nephritis assumed an increasing importance.

MacLeod and I, while examining a group of supposedly normal soldiers, laid special emphasis on the presence of albuminuria, the urinary secretion and the blood pressure. In these individuals there was no other factor which could be considered as possibly influencing the future development of nephritis. Latent albuminuria has more frequently made its appearance in the soldiers stationed in the trenches and in those who have just come from the trenches than in the men who are working behind the lines. In the French army I found albuminuria in 1.66 per cent of the active troops, while less than 1 per cent of those engaged in the more peaceful pursuits in the barracks, etc., gave evidence of this abnormality. In the British forces MacLeod demonstrated that 4.73 per cent of the men in the trenches showed albuminuria, while only 2.91 per cent of those behind the lines were found positive. This latent albuminuria in the soldiers behind the lines is chronic in character and is secondary to chronic renal lesions. On the other hand, those who are actively engaged in the trenches have what is evidently a "fatigue albuminuria," which disappears almost immediately when they cease their active duties. MacLeod found that 10.12 per cent of the recruits undergoing intensive training in England had an albuminuria.

We soon became aware of the fact that these albuminurias are not an indication that these subjects are predisposed to nephritis. Three men whose urine MacLeod had analyzed two weeks previously and found to be free from albumin, gave evidences of a nephritis later, one of them being a fatal case.

The blood pressure of the men engaged in trench warfare does not differ from that of the men in military service but not in the line.

The elimination of urea, chlorides and water in the urine is the same both in quantity and concentration in both groups. In the English army the amount of urea eliminated day by day per individual is about 50 per cent greater than among non-combatant French troops, and a little more than three times as large as the average amount eliminated by the active French soldier.

Pathogenic theories. Beyond a few inadequate and self-evident facts, there are only contradictory and empty hypotheses which may be called upon to explain the immediate cause of war nephritis. The etiology of this disease is certainly a perplexing one; unfortunately, up to the present time it remains unsolved. The theories advanced for the solution of this problem may be classified under four principal headings:

1. *The meteorological theory*, if one may call it such; exposure to cold has been regarded by many as the responsible factor.

2. *The toxic theory.*

3. *The theory of renal impairment.*

4. *The theory of infection.*

1. *Exposure to cold* has for a long time been supposed to result in nephritis. Germany is the only country in which this etiological factor has been considered. Chiari and Bruns maintain in no uncertain terms that it is almost always the chief cause. Bruns says that in 70 per cent of the patients there is a clear history of a chill or exposure to dampness and cold. This hypothesis is not borne out by the conditions under which this illness has occurred. Nephritis did not appear in our army during the winter, but in the spring among the British troops and in the summer among the French. As Langdon Brown maintains, this theory must be entirely abandoned when it becomes apparent that the cases of nephritis assume more marked proportions as the warm weather sets in. A study of the statistics obtained during other wars confirms this observation. Nephritis was infrequent in the South African war in spite of enormous fluctuations of temperature (at 6 a.m. the weather was cold enough to result in a hoar frost, whereas at half-past three in the afternoon mirages made their appearance).

In spite of wide ranges of temperature there were no cases of nephritis in the Russo-Japanese war. Furthermore, in the American Civil War nephritis appeared during March and continued for one year; subsequently it diminished and remained about constant as regards the number of cases observed during the remaining years of the conflict. When these patients are questioned closely they will always say that they have been

exposed to cold; in most instances this is purely a subjective matter, and the sensation experienced by the patient corresponds to a slight initial febrile rise which is not noted by the physician in charge.

2. *Intoxication.* This factor at first seemed to be of great importance, since the appearance of cases of nephritis in large groups appeared to point in this direction. Very careful research has been done in order to ferret out toxic substances in the drinking water, or to discover mineral poisons which may have been ingested and were being excreted in the urine.

At first at least, many thought that the chlorinated water might have a detrimental effect on the kidneys. Since, however, the French soldiers for the most part drink nothing but wine, this argument necessarily falls to the ground. It must be remembered also that the water used in cooking the food and in the preparation of coffee is rarely of the chlorinated variety.

Mackenzie Wallis has searched for mineral poisons in the tablets used in the sterilization of water, in the water of the canteens, and in the urine of nephritic patients. In the latter he was able to find traces of arsenious acid (in proportion of 1:1,000,000), and less marked traces of antimony and mercury.

Powell-White was of the opinion that possibly lead might be responsible, because of the considerable consumption of tinned food. He analyzed the urine of four patients with trench nephritis, and he was always able to find traces of lead; in other instances he found tin. The urine of normal individuals does not contain even traces of this metal.

Inasmuch as the whole army is subject to these conditions which are supposed to cause nephritis through intoxication, it is necessary to reject all of them as explanations. This is very evident when we consider the fact that among these men, all living under the same conditions, certain groups, such as the officers, are apparently immune.

3. *Renal impairment.* It may be possible that the kidney yields, little by little, to the unfavorable conditions which the soldier's life imposes upon it. It is very likely that the renal organs are changed so that they readily fall prey to pathogenic

influences which under ordinary circumstances they throw off without difficulty. It becomes pertinent to ask oneself if the abnormal conditions created by the war do not render the kidney less resistant to the stress and strain imposed by the many minor ailments which cause no noticeable impairment of health. Physical overwork, insufficient sleep, abnormal food, and constant exposure to inclement weather, are some of the factors which have to be reckoned with.

Among the causes of renal impairment the great importance of diet has often been emphasized. Albu and Schlesinger believe that this is the main etiological factor. The food is usually far too heavy. It is given for the greater part in concentrated form or in cans, and contains much salt and little fat. In France the soldier's diet has been criticised as containing too much meat. It was thought that food too rich in protein might disturb the kidney, not so much by its direct action on the kidney, but, as Buchard and Robin showed, through the excessive production of toxic products of putrefaction formed in the gastrointestinal tract which reach the kidney by way of the blood. Mackenzie Wallis has shown that the ethereal sulphates (such as indican), found in the urine, are not increased in the cases of acute nephritis. Thanks to the work of Ambard and Papin, we know a few facts concerning the production of nephritis through alimentary causes. They have shown in dogs that the maximal concentration of urea in the urine, brought on by high meat diet, may result in a nephritis. It is possible that this is responsible for at least a part of the nephritis under present conditions. The average concentration of urea in the urine is higher in the English than in the French soldier (24.4 grams per litre for the former, 12.35 grams for the latter). The average daily output is also higher among the English troops than among our men (45.03 grams for the English, 14.44 grams for the French). Finally, it is uncommon to find a urea concentration which approaches the maximum in the urine of French soldiers; that is, a concentration of 30 grams per litre or higher. On the other hand, among the British troops we have found 25 per cent who had a concentration above 30 grams. It may be that this fact

explains the more frequent occurrence of transient albuminuria and the greater prevalence of nephritis in the British army.

4. *The rôle of infection.* It would seem that infections are responsible in great part, if not entirely, for the occurrence of war nephritis.

Up to the present time the bacteriological results have not been very promising. Blood cultures have proved to be negative in the hands of all observers. M. H. Gordan and I have made very many aerobic and anaerobic cultures with absolutely no success. There is one possible exception to this, inasmuch as in one case of nephritis with jaundice I was able to isolate the paratyphoid B. bacillus. The blood of this patient agglutinated the same organism. In another instance of the same kind, Pagniez, in a patient who had not been vaccinated, demonstrated an agglutination in a dilution of 1:1,000.

Except for these two instances the bacteriological findings have yielded no important results. Gordon could not find positive agglutination reactions with the meningococcus. The Wassermann reaction is not more frequently positive in the cases of nephritis than it is in other patients.

Klein and Pulay in Vienna, and MacWalter in Dublin, attributed an etiological significance to the colon bacillus, which they discovered in the urine of these nephritics. It must be recognized that the colon bacillus is commonly present in the anterior urinary passages, and that it is not usual to find it in many of these cases. Other bacteria present in these urines are usually contaminations.

Mackenzie Wallis injected urine and serum of nephritics into rabbits and monkeys. He obtained the following results even when small doses were used: The immediate toxic effects are very transitory, but subsequently, after there has been a period of normal health lasting about eight days, signs of general malaise became manifest, and in two cases albuminuria appeared and death occurred within forty-eight hours. Autopsy revealed no changes in the kidneys. If the urine was warmed to 55 degrees for the half hour before injection, no effect could be noted. If the urine was placed in a collodion sack, allowed to dialyze,

and the concentrated product remaining within the sack was injected, more marked effects were produced than if the untreated urine was employed. These very important discoveries seem to me to hold much promise for the future.

In spite of the meager results yielded by bacteriological researches up to the present, it remains probable that the rôle of infection is an extremely important one. The inflammatory nodules found in the kidneys and other organs, and the febrile course of the disease, point to an infection as the probable cause.

When nephritis was first observed, it was thought that it might be a complication occurring in the course of undiagnosed acute infections which ran an abortive course. It was believed that such infections as scarlet fever and diphtheria might remain unrecognized. However, diphtheria is not nearly as frequent as nephritis in our armies, and scarlet fever has been very rare. Furthermore, throat cultures have always been negative, and in convalescents from nephritis the complications which could be ascribed to diphtheria or to scarlet fever, such as paralysis or desquamation, have been entirely lacking.

Attention has also been given to the possible effect of anti-typhoid vaccination. It must be acknowledged that there are such instances, but they are very few, and as far as I know, they are never of the edematous type. Such cases are of the azotemic type, and their azotemia is much more persistent, their Ambard's constant is impaired for a much longer period, than in the nephritics that we have described in this paper. The condition manifests itself almost immediately after the injection of the anti-typhoid vaccine. It should also be noted that a large number of cases of nephritis have been observed in individuals who have not been vaccinated.

It is possible to conceive that the predisposing factors for nephritis are precisely those which have been dealt with in the paragraph headed "Renal impairment." It must be admitted that the causes may be even more numerous than those that have been detailed. In some instances war nephritis was preceded by an angina. In one case this was of a phlegmonous char-

acter, caused by the streptococcus; in another case it was a simple erythematous sore throat. The post-mortem examination of the latter case revealed the streptococcus in the peritoneum, the spleen, and the kidneys, as MacLeod and I were able to demonstrate. Other cases followed a febrile dysentery or a severe parasitic ecthyma. One patient developed a nephritis fifteen days after the onset of a cerebro-spinal meningitis brought on by the diplococcus of Weichselbaum; in this case a definite cure had been brought about by the appropriate serological methods. It is apparent from these instances that more than one infectious cause is concerned in the production of war nephritis.

It may be that with the novel conditions brought about by the war, micro-organisms which were ordinarily unheard of assume importance. The digging of trenches and throwing up of earthworks on so vast a scale may have brought forth great numbers of them. If we are prepared to admit that war nephritis is caused by a single specific infectious agent, the question of contagion must be seriously considered. We must recognize the fact that of all the men behind the lines it is only the hospital nurses who are exposed to it. If we are dealing with a contagious disease, we should not reject the term "epidemic nephritis," which has sometimes been used.

We have shown that pure azotemic nephritis, and even nephritis with jaundice, are not clinically and anatomically identical with edematous nephritis. It appears probable that nephritis with jaundice and cases of hepato-nephritis are caused in nearly every instance by the spirochaeta icterohaemorrhagica. The negative cases may be readily explained by the difficulty in finding this organism, which is present only in certain stages of the disease in the urine and in the blood. Furthermore, it may not be possible to demonstrate it by the unreliable method of injecting it into a guinea pig. It is probable that azotemic nephritis without edema and without jaundice is brought about by one and the same cause. It is not impossible that it may

ultimately be proved that edematous nephritis is the result of this or a similar cause.³

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³ It pleases me very much to see that this hypothesis, which I had previously advanced on the 22d of December, 1916 (before the Société médicale des Hôpitaux) is substantiated by the researches which have come to my notice while I was correcting the proof of the present article. Salomon and R. Neveu have demonstrated in three cases of acute edematous nephritis the presence of a spirochete which, morphologically at least, resembles the spirochete of hemorrhagic icterus. (Société de biologie, March, 1917.)

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URINARY ANTISEPSIS—FURTHER STUDIES OF THE ANTISEPTIC PROPERTIES AND THE RENAL EXCRETION OF COMPOUNDS RELATED TO PHENOLSULPHONPHTHALEIN

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The ideal internal urinary antiseptic must be a drug which is chemically stable, non-toxic and non-irritating to the urinary tract; which is antiseptic in high dilution in urine, regardless of the reaction of the latter; and which is eliminated unchanged in high percentage by the kidney. There is no such drug known. A consideration of the properties possessed by phenolsulphonphthalein, however, shows that this compound comes very close to filling all the above requirements. Phenolsulphonphthalein is chemically stable, non-toxic, and non-irritating; and is eliminated by the kidney with almost incredible rapidity and completeness; but it has no antiseptic properties, excepting in water in its free acid form. (Clinically it is used as the mono-sodium salt.) This remarkable compound, synthesized in 1898 by Sohon, at Remsen's suggestion, investigated later in Abel's laboratory, and introduced into clinical use by Rowntree and Geraghty twelve years later, has become the most widely used and the most satisfactory of all the tests of renal function. This is due to the remarkable rapidity and completeness with which phenolsulphonphthalein is eliminated by the kidney, to its non-toxicity and to the ease with which it lends itself to colorimetric estimation. As evidence of non-toxicity, Rowntree and Geraghty have given one-gram doses to dogs without evidence of renal injury. Its marvelous rapidity and completeness of elimination is realized when one considers that a 6 mgm. dose, given intravenously, and therefore diluted about one mil-

lion times by the blood stream, appears in the bladder in about two minutes, and after one hour 60 to 70 per cent has been excreted by the normal kidney. Furthermore, about 30 to 35 per cent of this amount appears during the first fifteen minutes, and about 40 to 50 per cent during the first half hour. In view of these remarkable properties it was thought worth while to attempt a modification of the phenolsulphonphthalein molecule, with the hope that an antiseptic compound might be produced which still retained the properties of the original drug. As the problem gradually increased in scope it was found advisable to investigate a large number of compounds distantly related to phenolsulphonphthalein, as well as those closely related. The total number of compounds experimented with at present is over two hundred, the antiseptic properties of which will be enumerated in subsequent publications. The following paper deals only with compounds closely related to phenolsulphonphthalein.

Although the literature contains no record of any attempt to synthesize an internal urinary antiseptic, various workers (following the pioneer work of Ehrlich in chemotherapy) have, during recent years, attempted to correlate chemical structure and physiological action and thus produce compounds with a desired specific therapeutic action. It is not the purpose of the present paper to discuss this literature. For an excellent summary of recent work done along the lines of chemotherapy, the reader is referred to publications of Lewis. The problem which Lewis and his co-worker, Krause, are investigating is analogous to the problem on urinary antiseptics outlined above, in that they started with a dye (trypan red) which possesses the peculiar property of becoming localized in the caseous centers of tuberculous masses, and experimented with numerous modifications of this compound, with the hope that one might be produced which would inhibit the development of the tubercle bacillus, and still retain the localizing tendency of the original compound.

Limited space does not permit a discussion of the urinary antiseptics in present use, and of the great need of a really efficient

drug for this purpose, which may be given either intravenously or by mouth and which will cause an inhibition of bacterial development in the urine, regardless of the reaction of the latter. For a complete résumé of this phase of this subject, and a discussion of the relative values of the various urinary antiseptics in common use the reader is referred to the paper published by Hinman in 1915. This paper will be freely quoted. Of the urinary antiseptics in common use, hexamethylenamine is by far the best, but has very definite limitations, owing mainly to the fact that an acid medium is essential for the liberation of formaldehyde. Furthermore,

The necessity of concentration, and time for the accumulation of formaldehyde in antiseptic amounts, largely destroys the value of the drug for kidney antiseptics; for bladder antiseptics in cases with polyuria or frequent urination, except when retention in some form is present; in cases of urinary fistula, notably post-operative prostatics during the period of incontinence, and in cases with continual bladder drainage as in true incontinence or with retention catheter; and for urethral antiseptics no matter what the infection. The greatest usefulness of hexamethylenamine is in bladder prophylaxis in cases in which the above urinary conditions are not present. . . . Methylene blue, in a dilution of 1: 150,000, will inhibit the growth of staphylococci.

This drug would therefore seem of value in this type of infection, but there has been no experimental work showing that methylene blue does not undergo modification either in the blood stream or in the urine so as to lose its antiseptic value, as has been shown (Davis) is the case with so many other compounds. Hinman states that "the value as internal urinary antiseptics of other substances such as salol, oil of sandalwood, salicylic, boric and benzoic acids, is very limited;" and concludes that there is no known drug with properties even approaching those of an ideal urinary antiseptic.

As stated above, an ideal internal urinary antiseptic must be chemically stable, non-toxic, antiseptic in urine regardless of the reaction of the latter, and must, like phenolsulphonphthalein, possess the property of high-percentage elimination. It is

quite possible that a compound that is not entirely non-toxic, but relatively so, might be suitable for the purpose. Provided that the renal elimination of a given compound is sufficiently rapid and complete, and provided that this compound causes bacterial inhibition in urine in sufficiently high dilution, it is conceivable that small doses might serve to produce urinary antiseptis, even though the compound be moderately toxic. Considering the general toxic effects on the animal organism that an antiseptic compound may be expected to have, and considering the possibility of injury to the renal epithelium, and of irritating effects on the lower urinary tract, one realizes the hopelessness of the problem if the synthesis of a *completely* harmless urinary antiseptic is the goal. The matter than resolves itself into a question of *relative* toxicity; that is, the attainment of a compound combining minimum toxicity with maximum efficiency, so that small but effective doses may be safely used. The value of such a drug, particularly in cases of chronic pyelitis, resistant to all treatment, and in cases of alkaline cystitis, where urotropin is of no avail, could not be overestimated.

METHODS OF INJECTION

Each compound was investigated with two objects in view; first, to determine the rate of elimination by the kidney; and secondly, to determine the antiseptic properties. Rabbits were used for injection purposes because (1) they are easily available and cared for in large numbers, (2) because the ear-vein is easily injected, and (3) because the urethra of the male rabbit is large and easily catheterized. The drugs were injected intravenously in 10 mgm. amounts in 1 per cent solution, and the rabbits catheterized after one hour. In the case of each drug a colorimetric estimation of percentage of excretion was made with the Hellige colorimeter, 10 mgm. of the drug diluted in 1000 cc. of water being used as a standard. In order to make certain that the total excretion for one hour was quantitatively recovered, the bladders of the rabbits were irrigated after catheterization, and the irrigation added to the urine obtained through the

catheter. The percentage of excretion of each compound was estimated by averaging the results of at least two injections on different rabbits. It would have been impossible to determine the rate of excretion of such a large number of compounds had it not been that nearly all of them were highly colored and hence readily detected in the urine. Colorless compounds were rejected, excepting a few in which the antiseptic tests were unusually promising.

BACTERIOLOGICAL TECHNIQUE

Antisepsis *in urine* is quite a different thing from antisepsis in water. As will be shown below, and in subsequent papers, there are numerous compounds which are germicidal in high dilution in water, but which lose this property entirely when diluted in urine, and which even permit the growth of organisms in urine when in relatively strong concentration. This astonishing fact has proved to be a great obstacle. It may be readily seen that the compound, the antiseptic power of which is due to its acid or basic properties, would become inert in urine on account of the buffer action of urinary salts.¹ Other compounds, containing ionic silver, become inert in urine because the silver is precipitated by the chlorides. There remain, however, a large number of drugs whose loss of antiseptic strength in urine is due to some unknown interfering action, the nature of which is as yet undetermined. It must not be understood that this loss of antiseptic power in urine is noted after the compound has been passed through the animal body, but it occurs when urine is added to the aqueous solution of the compound in a test tube. For this reason it became necessary to carry on parallel germicidal tests both in urine and in water.

The colon bacillus was used throughout the experiments because it is the most frequent invader of the urinary tract, be-

¹ The term "buffer action" refers to the ability of mixtures of certain acid and alkaline salts in solution to maintain a practically constant hydrogen ion concentration, in spite of the addition of moderate amounts of acid or alkali. For detailed discussion, see publications of Henderson and Palmer, Clark and Lubs, and Shohl and Janney.

cause it is resistant to antiseptics and is readily cultivated. The particular strain used was one isolated from a case of chronic pyelitis. Investigations with other organisms are to be carried on in the future. Each compound was studied with the view of determining (1) its germicidal properties (in water and in urine) and (2) its antiseptic or inhibitory properties in urine.

1. *Germicidal test.* In order to rule out a large number of undesirable compounds it was necessary to establish an arbitrary standard of germicidal strength, and compare them all with phenol. The arbitrary method chosen was the determination of the highest dilution of each compound which, in 1 cc. amount, will kill one loop (3 mm. internal diameter) of a twenty-four hour broth culture of colon bacillus, in one hour, at 37°C. Dilutions of the drug were made with sterile pipettes in sterile test tubes, and all but one cc. of each dilution discarded. After inoculating each dilution with one loop of colon bacilli, and incubating for one hour, 0.1 cc. of each was transferred to melted agar, and plated. In transferring these 0.1 cc. amounts, it was found convenient to use capillary pipettes drawn out (from 3 mm. glass tubing) long enough to reach the bottom of the test tubes. By connecting the large end of one of these capillary tubes to a carefully calibrated small syringe (by means of a small rubber tip), it was found that 0.1 cc. amounts could be drawn up with remarkable accuracy, irrespective of variations in the size of the capillary tubes. These tubes were used over and over again, large numbers being sterilized together by means of dry heat.

Parallel tests were run for each compound, using sterile water for one series of dilutions and sterile urine for the other. It was found to be unnecessary to adopt any method of sterilizing the urine to be used for this purpose. Agar plates poured each day containing 0.1 cc. of urine taken from a specimen voided in a sterile (second) flask by a normal individual, were uniformly sterile. (Although these agar plates, inoculated with 0.1 cc. of fresh urine, showed no growth, it would be incorrect to say that the entire specimen of urine was sterile, for a profuse growth of cocci always developed, after twenty-four hours' incubation.

Hort, in 1914, carried out an extensive careful series of experiments along these lines and concluded that "the sterility of normal urine in man still awaits demonstration," although, by suprapubic aspiration, he was able to obtain sterile urine from animals.) The factor of possible error due to modification of the urine through the process of sterilization was thus eliminated. For example, sterilization of urine by heat produces a marked change in the hydrogen ion concentration, the urine becoming much more alkaline.

The effect of the reaction of the urine in aiding or hindering the germicidal activity of a drug is an all-important factor. Henderson and Palmer have shown that the hydrogen ion concentration of urine is normally subject to a considerable range of variation (p_H 4.8 to p_H 7.4), and that the average of this range is p_H 6.0 on the hydrogen ion scale, corresponding to 0.000001 N acid.² The importance of the reaction of urine when used as a culture medium has been pointed out by Shohl and Janney, who find that the colon bacillus fails to grow in urine at certain definite acid (p_H 4.8) and alkaline (p_H 9.2) end-points. In order to eliminate possible error, due to strongly acid or alkaline urine, the hydrogen ion concentration of each specimen of urine to be used for antiseptic experiments was determined, and the specimen rejected if the reaction was not approximately that of average normal urine, that is, p_H 6.0.

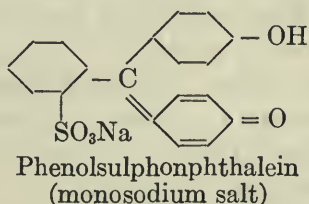
2. *Antiseptic test.* More important than the determination of the germicidal strength of these compounds, was the determination of the highest dilution of each *in urine* that will cause an inhibition of bacterial development. For this, dilutions in urine were made in 1 cc. amounts, using sterile test tubes. Each tube was inoculated (as in the germicidal test) with one standard loop of a twenty-four-hour broth culture of the colon bacillus, immediately after which 0.1 cc. of each inoculated dilution was plated, as proof that the inoculation had been made, and for the purpose of comparison with a second plate which was poured

² For discussions concerning the hydrogen ion concentration of urine and the technique for the colorimetric estimation of same, see papers by Clark and Lubs, Henderson and Palmer, and Shohl and Janney.

(again transferring 0.1 cc.) after the inoculated dilutions had been incubated for twenty-four hours at 37°C. Contrasting these two plates, poured at twenty-four-hour intervals, showed whether or not growth had taken place during the incubation period. The first plate (poured immediately after inoculation) usually¹ showed about 10,000 colonies, roughly estimated. A second (twenty-four-hour) plate which was sterile, or which contained very few colonies, (less than 100) was considered proof of inhibition, while a plate showing countless numbers of colonies proved the absence of inhibition. In the vast majority of instances the contrast between the plates 1 and 2 was so marked that there could be no possible doubt. A daily control of inoculated drug-free urine invariably contained countless numbers of colonies in the second (twenty-four-hour) plate, showing that normal urine acts as a favorable culture medium for the colon bacillus.

PHENOLSULPHONPHTHALEIN AND SALTS

The properties of phenolsulphonphthalein itself, and of some of its metallic salts (sodium, silver, copper, mercury and barium), as illustrated by the following structural formula, were first investigated.



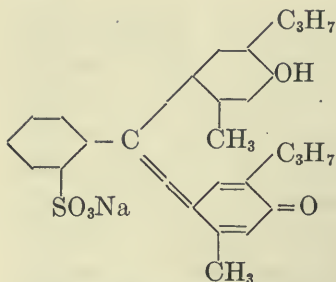
Phenolsulphonphthalein, in its free acid form, although almost insoluble, is nevertheless germicidal (against the colon bacillus, according to the arbitrary standard described above), in a dilution of 1:1000; that is it has about 50 times the strength of phenol. In urine, however, even in almost saturated solution, phenolsulphonphthalein permits the growth and development of the colon bacillus. A suggested explanation of this loss of power is that the watery solution kills by virtue of its acidity,

whereas in urine the acid properties are lost on account of the buffer value of the urinary salts. Furthermore, the mono-sodium salt, the form used clinically, has no germicidal action even in water, and in urine permits the growth of colon bacillus even in a 1:200 dilution. The silver salt is extremely germicidal in water (having 5000 times the strength of phenol), but in urine the silver is precipitated by the chlorides, and the germicidal strength, due to the silver ion, is lost. The fact that the chlorides are responsible is shown by a similar disappearance of germicidal action when the dilutions are made in normal saline solution. Furthermore, when the silver salt is injected intravenously the ionic silver is lost in the body and the phenolsulphonphthalein appears in the urine free from silver, probably as the sodium salt. The germicidal properties of the silver salt of phenolsulphonphthalein, both in water and in urine, correspond very closely to those of silver nitrate. Mercurous and mercuric salts and the cupric salt, although having some germicidal value in urine, were discarded because of their toxicity. The barium salt was quite inert.

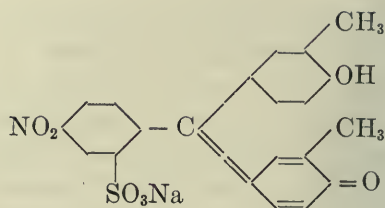
Conclusion. The metallic salts of phenolsulphonphthalein give no promise of value as urinary antiseptics.

SULPHONPHTHALEINS

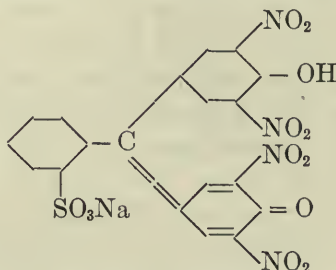
The compounds listed in table I are all analogous to phenolsulphonphthalein, differing from the latter compound only by the presence of various substituent groups (OH, CH₃, NO₂, NH₂, C₃H₇, COOH), as illustrated by the three following representatives. All but three of these compounds are only slightly soluble in water, as the free acid, but are readily soluble in the form of the sodium salt. In the case of the substances insoluble in water, solution was effected by adding to a weighed amount of the dye tenth normal sodium hydroxide in amount just sufficient to dissolve the dye. The resulting solution contained the monosodium salt. Tetra-aminophenolsulphonphthalein was used in the form of its hydrochloride. Pyrocatechinsulphonphthalein and guaiacolsulphonphthalein are sol-



Thymolsulphonphthalein



Cresolparanitrosulphonphthalein



Tetranitrophenol-sulphonphthalein

uble in water without the addition of alkali, as is the hydrochloride of tetra-aminophenolsulphonphthalein. Some of these compounds are quite germicidal in water (possibly due to excess alkali necessary to bring them into solution), but with the exception of one only, it is a uniform rule that they lose this action when diluted in urine. Pyrocatechinsulphonphthalein, the only one to retain its value, is germicidal in urine in a dilution of 1:500 and inhibitory in urine in a dilution of 1:1000.

Very surprising results were obtained by the injection of these compounds. Although they are all quite closely related chemically, some of them are eliminated by the kidney with the same marvelous rapidity and completeness as is phenolsulphonphthalein, while others appear in the urine only in traces or not at all. The excretion seems to be governed by no rule. With this class of compounds, no definite relationship between chemical structure and "renal affinity" could be established. The addition of methyl groups to the phenol nucleus (cresolsulphonphthalein)

TABLE I
Sulphonphthaleins

NAME	ANTISEPTIC STRENGTH				EXCRETION—PERCENTAGE AFTER 1 HOUR	
	In water	In urine				
		Dilution which kills B. coli after 1 hour	Dilution which kills B. coli after			Dilution which permits growth
			1 hour	24 hours		
Phenolsulphonphthalein.....	※ *	※	※	1:200	70	
Thymolsulphonphthalein.....	1:200	※	※	1:200	Trace	
Thymolparanitrosulphonphthalein...	※	※	※	1:200	Trace	
Cresolsulphonphthalein.....	※	※	※	1:200	70	
Cresolparanitrosulphonphthalein....	※	※	※	1:200	50	
Salicylsulphonphthalein.....	※	※	※	1:200	Trace	
Hydroquinonesulphonphthalein.....	※	※	※	1:200	40	
Pyrogallolsulphonphthalein.....	※	※	※	1:200	30†	
Pyrocatechinsulphonphthalein.....	1:2000	1:500	1:1000	1:2000	0	
Guaiacolsulphonphthalein.....	1:200	※	※	1:200	Trace	
Tetranitrophenolsulphonphthalein ...	※	※	※	1:200	Haemoglobin-uria	
Tetra-aminophenolsulphonphthalein	1:200	※	1:200	1:500	0	
Alphanaphtholsulphonphthalein.....	1:200	※	※	1:200	Unstable	
Phenol.....	1:180	1:180	1:800	1:1000		

* In this and following tables, ※ indicates that a 1:200 dilution failed to kill.

† When the urine, after injection of pyrogallolsulphonphthalein, was made alkaline, an evenly distributed blue color appeared, and the above estimate of excretion was made upon the urine in this condition. Upon standing, however, the phosphates which settled out carried the coloring matter along with them, and the supernatant liquid was quite colorless. This phenomenon, which is doubtless due to absorption, is unique among all the dyes studied. The same result was observed when pyrogallolsulphonphthalein was added to urine, and the latter, after the addition of alkali, was centrifuged. This shows that the peculiar behavior is not due to any change that the dye may have suffered during its passage through the organism.

certainly does not interfere with excretion, while the addition of the isopropyl groups (thymolsulphonphthalein), amino group (tetra-aminophenolsulphonphthalein) and carboxyl groups (salicylsulphonphthalein) prevents excretion.

The most interesting feature shown by the sulphonphthaleins is the effect of the addition of OH groups to the phenol nucleus.

Pyrogallolsulphonphthalein, hydroquinonesulphonphthalein and pyrocatechinsulphonphthalein are all hydroxyl derivatives, differing only in the number and position of the substituent hydroxyl groups, and, of these, the pyrogallol and hydroquinone compounds are excreted, whereas pyrocatechinsulphonphthalein, the only sulphonphthalein shown to be antiseptic in urine, unfortunately, is also the only one not excreted.

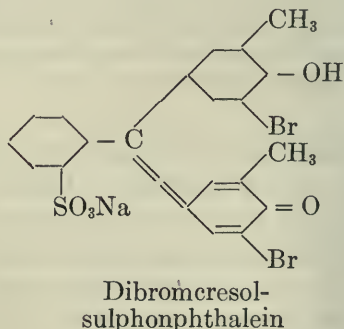
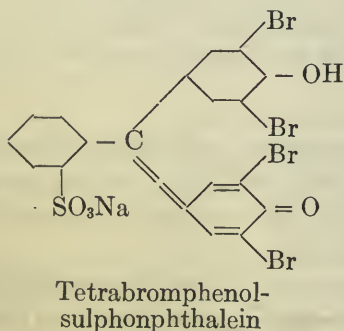
It is probable that this substance is not a simple phthalein, but that it contains more than the normal two pyrocatechin residues in combination with the sulphobenzoic acid residue. An analogous compound, which was shown to contain *eight* pyrocatechin residues, was prepared by Lyman and Gilpin. This difference between pyrocatechinsulphonphthalein and the other sulphonphthaleins probably accounts for the unique behavior of this substance as compared with the others of the series, as regards germicidal action in the urine.

Conclusions. (1) Several sulphonphthaleins other than phenol-sulphonphthalein are excreted by the kidney with great rapidity.

(2) None of the sulphonphthaleins investigated would be of value as a urinary antiseptic, since the only one showing antiseptic strength in urine fails to be excreted.

HALOGEN DERIVATIVES OF SULPHONPHTHALEINS

To illustrate the chemical structure of the halogen derivatives of sulphonphthaleins investigated (see table 2) the following formulae are given:



These compounds, all used in the form of the sodium salt, show moderate germicidal activity in water, possibly due to excess alkali necessary to bring them into solution, but they all become inert in urine. The *bromine* derivatives are not excreted, but the substitution of *chlorine* does not seriously interfere with excretion, tetrachlorophenolsulphonphthalein being excreted to the extent of 35 per cent in one hour. Di-iodophenolsulphonphthalein is excreted in a changed form of some kind, the color of the alkaline urine being much like that of phenolsulphonphthalein, whereas the di-iodo derivative as injected has a deep blue purple color. On this account, the colorimetric estimation of the amount of this compound eliminated was not possible. The substitution of the halogens therefore shows a definite relationship between the chemical composition and "renal affinity."

Conclusions. (1) Substitution of bromine in compounds of the sulphonphthalein type prevents excretion by the kidney, but substitution of chlorine merely decreases the percentage of elimination.

(2) Halogenated sulphonphthaleins give no promise of value as urinary antiseptics.

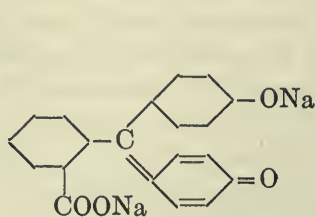
TABLE 2
Halogenated sulphonphthaleins

NAME	ANTISEPTIC STRENGTH				EXCRETION—PER- CENTAGE AFTER 1 HOUR	
	In water	In urine				
		Dilution which kills B. coli after 1 hour	Dilution which kills B. coli after			Dilu- tion which permits growth
			1 hour	24 hours		
Tetrabromphenolsulphonphthalein...	※ *	※	※	1:200	0	
Tetrachlorphenolsulphonphthalein...	1:1000	※	※	1:200	35	
Di-iodophenolsulphonphthalein.....	1:1000	※	※	1:200	Excreted in changed form	
Dibromcresolsulphonphthalein.....	1:200	※	※	1:200	0	
Dibromthymolsulphonphthalein.....	1:200	※	※	1:200	0	

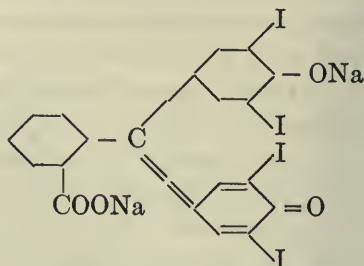
* ✗ indicates that a 1:200 dilution failed to kill.

PHTHALEINS

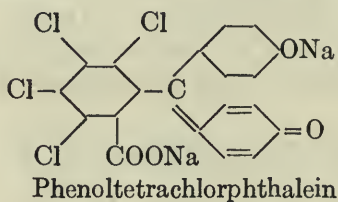
These compounds, listed in table 3, differ from sulphonphthaleins in that a carboxyl group replaces the sulphonic acid group, as shown by the following formulae:



Phenolphthalein



Tetraiodophenolphthalein



Phenoltetrachlorophthalein

TABLE 3
Phthaleins

NAME	ANTISEPTIC STRENGTH				EXCRETION—PERCENTAGE AFTER 1 HOUR	
	In water	In urine				
		Dilution which kills B. coli after 1 hour	Dilution which kills B. coli after			Dilution which permits growth
			1 hour	24 hours		
Phenolphthalein.....	1:200	※ *	※	1:200	Trace	
Thymolphthalein.....	1:200	※	※	1:200	0	
Tetrabromtetrachlorphenolphthalein.....	1:200	※	※	?	0	
Tetra-iodophenolphthalein.....	※	※	※	1:200	Trace	
Phenoltetrachlorphthalein.....	1:200	※	※	?	Trace	
Sodium phenolphthalein trisulphonate.....	1:200	※	※	1:200	65	

* ※ indicates that a 1:200 dilution failed to kill.

The most notable chemical differences between the two classes of substances are: (1) the phthaleins are colorless and are nearly insoluble in water, as free phthaleins, whereas the sulphonphthaleins are colored and fairly soluble in water; (2) the phthaleins are weak acids and form comparatively unstable salts, whereas the sulphonphthaleins, as shown by White and Acree, are very strong acids and form stable salts; (3) the phthaleins form *only* dibasic salts, whereas the sulphonphthaleins form monobasic or dibasic salts.

TABLE 4
Xanthones

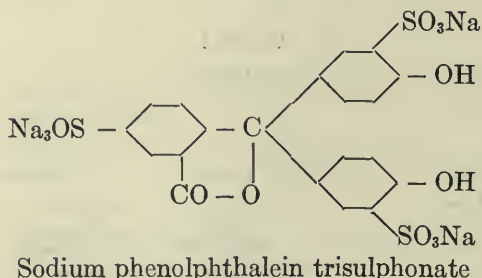
NAME	ANTISEPTIC STRENGTH				EXCRETION*—PERCENT—AGE AFTER 1 HOUR	
	In water	In urine				
		Dilution which kills B. coli after 1 hour	Dilution which kills B. coli after			Dilution which permits growth
			1 hour	24 hours		
Resorcinphthalein (Fluorescein)....	% †	%	%	1:200	90	
Resorcinsulphonphthalein (Sulphonfluorescein).....	%	%	%	1:200	75	
Orcinsulphonphthalein.....	%	%	%	1:200	70	
Resorcinsaccharein.....	%	%	%	1:200	70	
Rhodamin.....	1:2000	%	%	1:1000	60	
“Mercury fluorescein”.....	1:100,000	1:8000	1:10,000	1:30,000	90	

* It has been mentioned in the text, and should again be emphasized here, that these estimates are only approximate, as the colorimetric determination of fluorescent substances is rather uncertain.

‡ ‡ indicates that a 1:200 dilution failed to kill.

None of the phthaleins was antiseptic in urine; nor was any excreted by the kidney, except phenolphthalein trisulphonate. It is interesting to note that the sulphonation of phenolphthalein gives a soluble compound (phenolphthalein sulphonic acid), the sodium salt of which is excreted almost as rapidly and completely as is phenolsulphonphthalein. The similarity of names, however, between this compound and phenolsulphonphthalein should not give the impression that the two are the same. They differ in composition, structure and method of preparation. Phenol-

phthalein trisulphonate was prepared by direct sulphonation of phenolphthalein. Its sodium salt is a white or slightly yellow powder readily soluble in water, giving a colorless solution. The analysis of the salt indicated the presence of three sulphonic groups. The position of these groups in the phenolphthalein molecule has not yet been determined, but the following tentative formula is given for purposes of comparison with phenolsulphonphthalein.



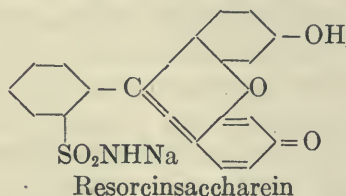
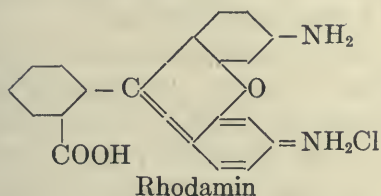
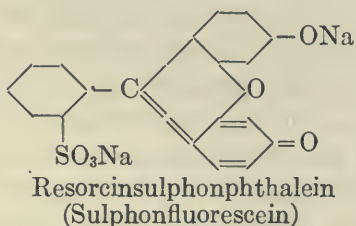
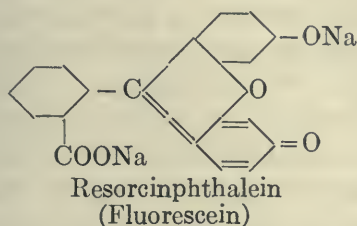
It is seen from this formula that the substance bears some relation to both phenolsulphonphthalein and phenolphthalein. It differs from both of them in the fact that it can be brought into solution in a colorless form, without the addition of alkali. The phenolphthalein exists in the solution in the lactoid form, and the phthalein molecule is present as the uncombined acid. Phenolphthalein trisulphonate is, in effect, merely "soluble phenolphthalein." The addition of alkali to this colorless solution produces the usual red color characteristic of phenolphthalein.

Since phenolphthalein trisulphonate is rapidly excreted, while phenolphthalein is not, the conclusion might be drawn that the sulphonic acid groups are essential to rapid elimination. However, this theory is upset by the action of the following group of compounds, the xanthenes, which demonstrate that the sulphonic group bears no *essential* relation to "renal affinity."

Conclusion. The phthaleins give no promise of value as urinary antiseptics.

XANTHONES

Compounds of this class, listed in table 4, are characterized by the fact that the two phenol groups are linked together by an oxygen atom, as illustrated by the following formulae:



It will be seen that although resorcinphthalein (fluorescein) differs from phenolphthalein only in the presence of an oxygen atom, the two compounds possess divergent biological properties. All of these compounds investigated have strong yellow-green or red-green fluorescence, and without exception they are excreted by the kidney with a rapidity as great as, if not greater than, that of phenolsulphonphthalein, the average rate of excretion for the group being about 70 per cent in one hour.³

Since these compounds differ from each other considerably in a chemical respect, but have one characteristic in common, viz., the oxygen atom linking two phenol groups, and since they all show great "renal affinity," it is reasonable to assume that we have here a definite relationship between chemical structure and physiological action. This class further shows that the sulphonic acid group is not essential for rapid excretion.

³ The estimation of the output of these substances is subject to some inaccuracy, as the colorimetric determination of fluorescent substances is a difficult matter.

As germicidal agents all are inert excepting rhodamine and "mercury fluorescein" each of which comes very close to filling all the requirements of the ideal urinary antiseptic. Rhodamine, which differs from fluorescein in that the two hydroxyl groups are replaced by amino groups, is chemically stable and non-toxic, is rapidly excreted, and kills the colon bacillus in one hour in a dilution of 1: 2,000, *in water*; but, when the compound is diluted in urine this property is entirely lost. An investigation of the nature of this interfering action in urine has not been completed, but present experiments indicate that the loss of antiseptic power of rhodamine in urine cannot be accounted for merely by the buffer value of the urinary salts, which would tend to neutralize any acid or basic properties that a drug might possess.

"Mercury fluorescein" is the most interesting compound yet studied, and very closely approaches the ideal. The name given is at present only tentative, and may be modified as the result of further chemical investigation on the material, which is now being carried out. Suffice it to say that the substance, which appears to be a perfectly definite chemical individual, is fluorescein containing organically bound mercury; that is, the mercury is present in a non-ionic form. The substance is chemically stable, is very rapidly excreted and is antiseptic *in urine*. Its toxicity has not yet been fully determined, and is at present being fully investigated. The results of this investigation, which is also including the action of other organic mercury compounds, will be the subject of a subsequent publication. With this compound however we have obtained a definite result, in that 5 mgm. doses, injected intravenously, have caused dogs to excrete urine which is *definitely germicidal for at least one hour following administration*. Furthermore, preliminary experiments have shown no injurious effects from this dosage.

HALOGENATED XANTHONES

The members of this class which were studied are shown in table 5. The chemical structure of these compounds will be obvious to the reader from the type formulae already given for

xanthenes and halogenation products of phthaleins and sulphon-phthaleins.

None of these substance showed any germicidal action in urine, and only "chloreosin" was excreted in more than traces. The excretion of this compound in considerable amount, together with the similar result obtained with tetrachlorphenolsulphon-phthalein, brings out strikingly the difference between the physiological properties of substituted chlorine as compared with substituted bromine.

TABLE 5
Halogenated xanthenes

NAME	ANTISEPTIC STRENGTH				EXCRETION—PERCENTAGE AFTER 1 HOUR	
	In water	In urine		Dilu- tion which permits growth		
		Dilu- tion which kills B. coli after 1 hour	Dilution which kills B. coli after			
			1 hour			24 hours
Tetrabromresorcinphthalein (Eosin).....	✱ *	✱	✱	1:200	Trace	
Tetrachlor-resorcinphthalein (Chloreosin)...	✱	✱	✱	1:200	30	
Tetra-iodoresorcinphthalein (Iodeosin).....	1:200	✱	✱	1:200	Trace	
Tetra-iodoresorcintetrachlorphthalein.....	1:200	✱	✱	1:1000	Trace	
Tetrabromresorcindichlorphthalein.....	✱	✱	✱	1:200	Trace	
Tribromresorcinsulphonphthalein.....	1:200	✱	✱	1:500	Trace	
Dibromdinitroresorcinphthalein.....	✱	✱	✱	1:200	Trace	

* ✕ indicates that a 1:200 dilution failed to kill.

SUMMARY

The property possessed by phenolsulphonphthalein, by virtue of which is it so rapidly eliminated by the kidney, is by no means limited to this compound. Several other more or less closely related compounds show the same striking "renal affinity," and might also be of value in testing renal function were it not that phenolsulphonphthalein itself is so nearly ideal for this purpose.

Compounds of the xanthone class, that is, phthaleins (though not necessarily sulphonphthaleins) in which there is an oxygen

atom linking the two phenol groups, show a similar remarkable "renal affinity."

The bromination of these compounds, both sulphonphthaleins and xanthenes, almost completely prevents the excretion, but chlorination merely diminishes the excretion. Iodination prevents excretion or gives rise to elimination of the substance in a modified form.

In view of the hitherto overlooked fact that numerous actively germicidal compounds lose their strength (due to an as yet unexplained cause) when simply diluted with urine in a test tube, the value of every drug used for the purpose of urinary antiseptics ought to be questioned until its antiseptic strength *in urine* has been experimentally demonstrated.

It has been possible to establish a certain relationship between chemical structure and renal excretion, and to predict, with a reasonable amount of accuracy, which drugs will and which will not be excreted. The synthesis of germicidal compounds, very closely related to the types excreted, has been accomplished; one of these compounds, rhodamine, was excreted and would have been satisfactory but for the interfering action of the urine; another compound "mercury fluorescein," has been found to be rapidly excreted and to produce germicidal urine.

It is hoped that these experiments may call attention to the inadequacy of the urinary antiseptics in general use, and stimulate interest in the possibilities offered by synthetic chemistry. The investigation is being continued and the properties of various related compounds are being studied. Some of these compounds are old and well known, and others are new and have been synthesized so as to contain various chemical groups which are known to possess desired biological properties.

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THE DEVELOPMENTAL STAGES OF THE HUMAN SEMINAL VESICLES

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From the time of Fallopius (1) who first described the occurrence and position of the seminal vesicles, until comparatively recent years very little study has been given either to their function or anatomical detail. An increasing importance has of late been accorded these structures largely through appreciation of the rôle of chronic suppuration in relation to various systemic disorders. The knowledge concerning the development of the seminal vesicles is strikingly meager, and with the exception of the work of Pallin (2) in 1901 who studied four embryos in serial sections, there are very few examples of original observation on their development. Lowsley (3) in 1912, reporting his work on the development of the human prostate gland, refers briefly to the embryology of the seminal vesicles, stating that at birth each vesicle consists of five lumina in the upper part, all of which communicate lower down, the end duct finally connecting with the ampulla of the vas deferens to form the ejaculatory duct. In a more detailed study (4) the histologic and morphologic changes occurring in the fetal stages of the seminal vesicles have been reported at length.

During the thirteenth week of intra-uterine life the first indication of the formation of the seminal vesicles is encountered. This is seen as a slight bulging or evagination of the lateral aspect of the Wolffian ducts at a level about 0.25 mm. above the beginning prostate gland. This out-pocketing is at first very slight and appears merely as a diverticulum of the Wolffian duct, having the same mucous lining, supporting membrane and sur-

rounding layers of undifferentiated mesenchymatous cells as the Wolffian duct itself. These out-pocketings appear simultaneously and vary only slightly in size and level of origin. Their lateral diameter at this stage is always greater than their perpendicular height. As the sections of the earliest stage are carefully studied a definite furrow of demarcation is noted between the out-pushing or vesicle and the Wolffian duct. The constricting isthmus even in this earliest stage gives the vesicle an almost pedunculated appearance.



FIG. 1. SPECIMEN 768C (CARNEGIE EMBRYOLOGICAL COLLECTION)

Fetus 80.3 mm. long, thirteen weeks old. Reconstructed drawing from 75 serial sections showing the evagination of the Wolffian ducts to form the seminal vesicles. $\times 50$.

Between the thirteenth and fourteenth week a very appreciable growth takes place, for at the latter time the structures have become branched or bifurcated organs and have a dimension of approximately 1 by 0.5 mm. The lateral measurement is still greater than the perpendicular as in the earlier specimen. The picture of the vesicle now shows a fairly long chief or proximal canal which joins the Wolffian duct practically at right angles. The distal extremity of the vesicle is forked or V-shaped, showing a very definite development of diverticula, while along the proximal canal the irregularities of early budding or pouch formation are readily made out. The histology of the vesicle has not changed perceptibly during this intervening period. Its

lining and its various diverticula are still continuous with that of the Wolffian duct as a single layer of mucous cells supported by a definite basement membrane surrounded by numerous layers (10 to 12) of undifferentiated mesenchymatous cells.

At the sixteenth week of intra-uterine life the seminal vesicles present the same general picture as observed in the previous specimen. The intervening time has produced simply a growth in the form and architecture already laid down, rather than the formation of new diverticula and out-pushings. The striking change during this period has been the increase in the height or anterior-posterior length of the organs. This new direction

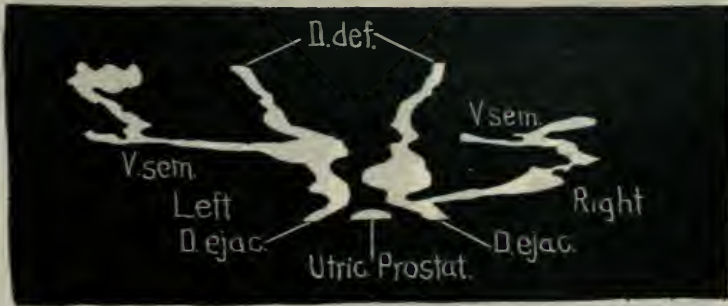


FIG. 2. SPECIMEN 1358E (CARNEGIE EMBRYOLOGICAL COLLECTION)

Fetus 105 mm. long, fourteen weeks old. Reconstructed drawing from 20 serial sections showing the seminal vesicles and Wolffian ducts. $\times 25$.

of growth has given to the vesicles an alignment more like their position at birth. It is worthy of note in this connection that every detail in the arrangement of their out-pocketings remains unchanged. The distal ends of the vesicles remain forked or bifurcated in two distinct and well formed channels which connect with the proximal canal or chief duct which is the original outgrowth from the Wolffian duct. The proximal canal is of about the same length as in the preceding specimen but shows in addition a more definite tendency to sacculation. The diameter of the proximal canal has increased in size and it here joins the Wolffian duct at an angle of about 45 degrees, which fact, accounts in a considerable measure for the increase in the anterior-posterior

length of the organs. The dimensions of each vesicle at this stage is a trifle over 1 by 0.75 mm. with the greatest length extending perpendicularly.

Between the sixteenth and nineteenth week a very notable growth takes place. This is evidenced by an increase in the number, and also by the marked irregularity and elongated growth of the sacculations of the middle and distal portions of the vesicles. At the latter date in this specimen the left vesicle consists of seven well formed separate channels of appreciable length which connect with each other or with the proximal canal

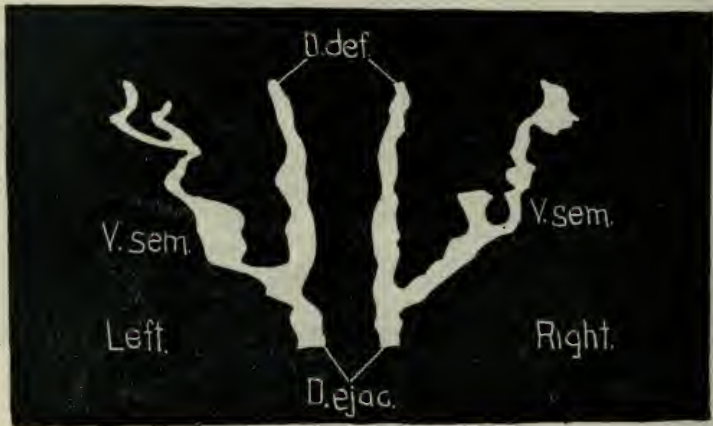


FIG. 3. SPECIMEN 1018 (CARNEGIE EMBRYOLOGICAL COLLECTION)

Fetus 130 mm. long, sixteen weeks old. Reconstructed drawing from 78 serial sections showing the seminal vesicles and Wolffian ducts. $\times 25$.

to form a very irregular branched organ. The right vesicle here shows only five elongated sacculations, but in other respects its general form, size and architecture are similar to its fellow of the opposite side. The proximal canals coming from the Wolffian ducts show in general no marked change from those of the previous specimen. They are still of about the same length but increased somewhat in diameter with a little more marked irregularity and a still greater tendency to sacculation and pocket formation. The Wolffian ducts in this specimen show a definite dilatation with beginning sacculation in the

region of the ampullae, which is the first indication of the future irregularity of this part to be noted in this study. The vesicles at this stage measure about 1.4 by 1.2 mm. in diameter, the right, being slightly longer in its anterior-posterior length, while the left has its greatest diameter laterally from the union with the Wolffian duct.

The next specimen studied at twenty-one weeks shows no appreciable growth in size of the vesicles but rather an overlapping or fusing of the elongated finger like processes already formed. This occurrence gives a picture in lateral view of wider, larger

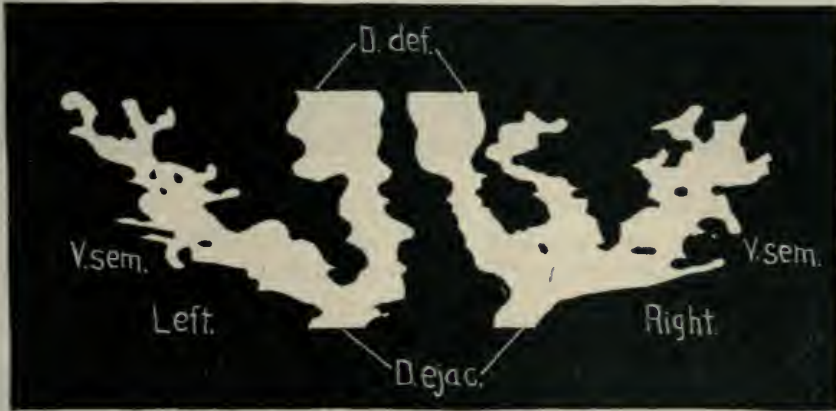


FIG. 4. SPECIMEN 1049 (CARNEGIE EMBRYOLOGICAL COLLECTION)

Fetus 171.4 mm. long, nineteen weeks old. Reconstructed drawing from 54 serial sections showing the seminal vesicles and Wolffian ducts. $\times 25$.

sacculations, which in many instances are simply superimposed out-pocketings. On the left side are encountered nine elongated diverticula and on the right seven similar out-pouchings. These are of varying size and length and many of them have their origin from the proximal canal, which has now notably increased in size, though still maintaining its same angle of position with the Wolffian duct. The region of the ampullae is here considerably dilated and somewhat irregular. The common ejaculatory ducts show no marked increase in size. The seminal vesicles at this time measure about 0.5 by 1 mm.

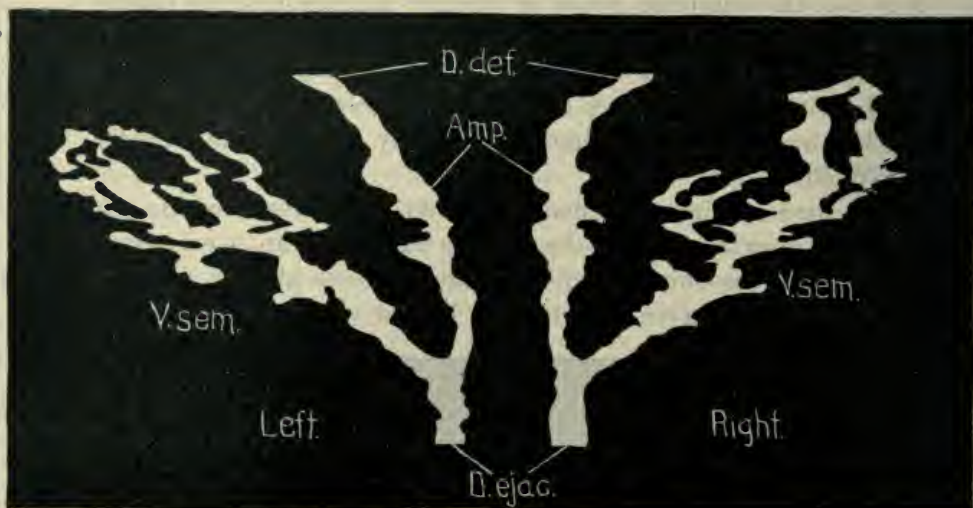


FIG. 5. SPECIMEN 1171 (CARNEGIE EMBRYOLOGICAL COLLECTION)

Fetus 178 mm. long, twenty-one weeks old. Reconstructed drawing from 22 serial sections showing the seminal vesicles and Wolffian ducts. $\times 25$.

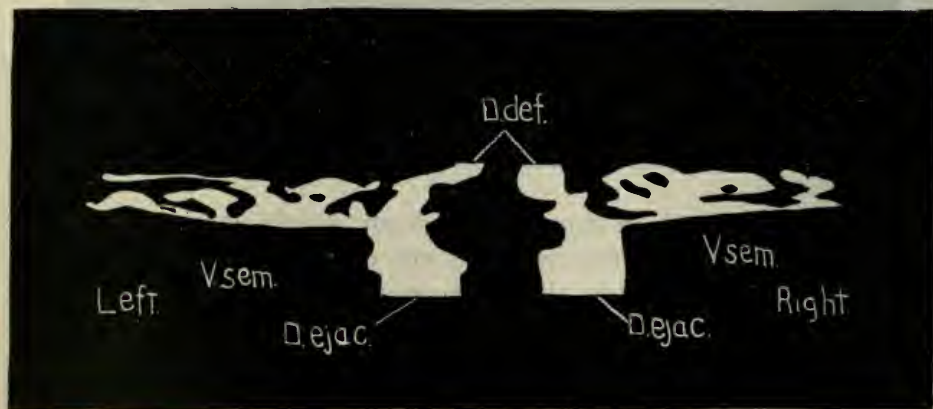


FIG. 6. SPECIMEN 1172 (CARNEGIE EMBRYOLOGICAL COLLECTION)

Fetus 221 mm. long, twenty-five weeks old. Reconstructed drawing from 16 serial sections showing the seminal vesicles and Wolffian ducts. $\times 12\frac{1}{2}$.

in diameter having the greatest dimension lateralward from the Wolffian duct.

At the twenty-fifth week of fetal life the architectural picture of the morphology of the vesicles presents only a few changes from that observed in the previous specimen. One appreciable difference at this time, as in the stage previously described, has been a reversion of position and dimension to the earlier fetal type, i.e., the greatest diameter extends lateralward from the Wolffian duct instead of perpendicularly as in some of the intermediate stages. Another point of difference has been the overlapping or superimposing of certain of the elongated branching sacculations, even more marked than in the preceding specimen, to give a picture of fewer, longer out-pouchings. This, however, is not necessarily the case, for while the lateral picture presents fewer branches, careful microscopic study through numerous serial sections shows that the individuality of the different canals is maintained throughout. At this stage the character of the sacculations has become more nearly the picture seen at birth. Their walls are well formed, composed of a very definite musculature and the lumen of each is larger than in any of the earlier specimens. Five elongated sacculations are encountered in the body of the left vesicle in this specimen, most of which arise from the proximal canal. In the right vesicle, also, five irregular elongated sacculations are noted some of which overlap yet maintain their individual lumina throughout. These, too, arise for the most part from the proximal canal, which, as with its fellow on the left side, is much shorter and of smaller caliber than in the previous specimen. The ampullae show considerable irregularity and sacculation while the common ejaculatory duct has markedly increased in size reaching very nearly the proportions observed at birth. The vesicles measure a little over 0.5 by 1 mm. in this specimen, the widest diameter being lateralward from the Wolffian duct.

Between the twenty-fifth and thirty-first weeks occurs the most marked growth and development of the vesicles. From all standpoints this is greater than during any similar period of fetal life. At the thirty-first week the vesicles appear as mark-

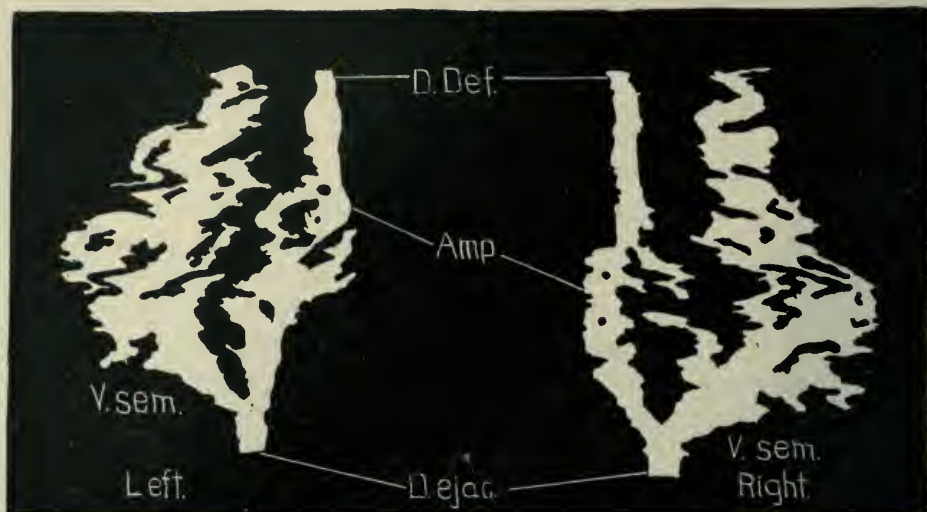


FIG. 7. SPECIMEN 7

Fetus 276 mm. long, thirty-one weeks old. Reconstructed drawing from 173 serial sections showing the seminal vesicles and Wolffian ducts. $\times 8$.

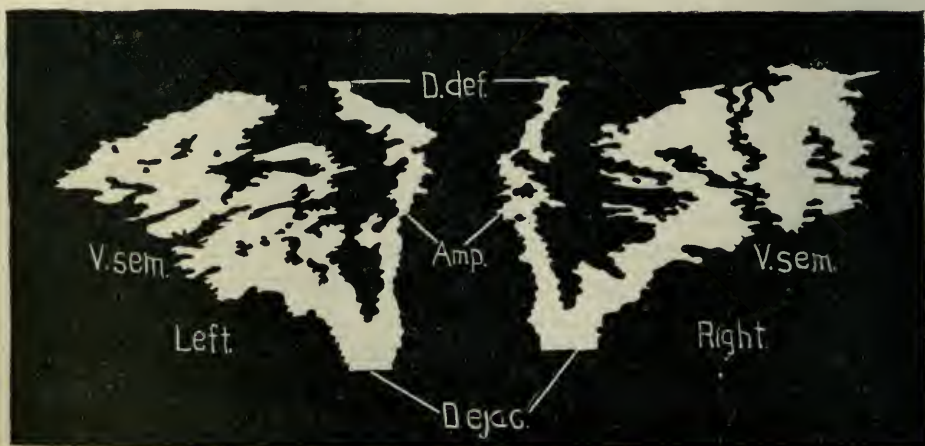


FIG. 8. SPECIMEN 8

Fetus 338 mm. long, at birth. Reconstructed drawing from 120 serial sections showing the seminal vesicles and Wolffian ducts. $\times 8$.

edly convoluted irregular organs. Their growth for the most part has been along the distal and middle portions and consists in an increase in size of all sacculations with much overlapping and in many places of an almost corkscrew like tortuosity. The vesicles in their perpendicular growth have come to lie almost parallel to the Wolffian ducts with many finger like processes projecting in all directions. The proximal canal, or practically the first third of the vesicle, remains in this specimen as in those previously described as a definite entity. This has increased notably in size during the last few weeks and is now somewhat funnel shaped with its apex forming the union with the Wolffian duct. The irregularity of the proximal canal is still present, though the definite elongated sacculations arising from it, at least in the portion nearest the Wolffian duct, are still very few. Forming the left vesicle can be counted ten rather large finger like processes springing from each other and from the proximal canal in a variety of forms. Each, however, maintains its individual canal from its origin to the end which is always a closed or blind pocket. The right vesicle also has ten somewhat similar branching finger like processes, thus making the structures in this specimen pretty well balanced organs yet differing notably in the detail of alignment. The vesicles in this specimen measure about 5.5 by 2.5 mm. in diameter, with the greatest length extending perpendicularly along the Wolffian ducts. The ampullae at this time present a picture of markedly dilated channels from which arise several (3 to 5) sacculated finger like processes in a variety of lengths and configurations. Each sacculation ends in a blind pouch but in every case its canal is patent throughout from its origin at the main lumen of the ampulla.

The last specimen studied in this series was a fetus at full term. Between the thirty-first week of intra-uterine life and birth a very considerable growth takes place. This, however, is not manifest as an increase in size of the vesicles but rather an increase in their irregularities and complexities of detail. The overlapping and superimposing of the various elongated sacculations have continued during the interval just passed until now

the lateral view of the vesicles presents a most ragged and irregular outline. This great irregularity of contour has taken place throughout the middle and distal portions of the body of the vesicle while the medial third or proximal canal remains practically unchanged. The body of each vesicle is in this specimen, at birth, composed of ten well defined main channels or diverticula. These are dilated pouches, some of which are of considerable length and width, while others are more shallow and arise from each other or from the proximal canal. In addition to these ten main channels or diverticula there are numerous saccules arising from the diverticula and proximal canal. The latter are shallow cup like depressions from the lumina of the canals which contribute greatly to the irregular outlines of the organs. The various channels are in direct continuity with each other throughout, and through the proximal canal finally join the ampulla which then becomes the common ejaculatory duct. At birth the main channels of the vesicle are in addition traversed by a net work of divisions which serve as a reticulated frame work for many of the saccules. The vesicles in this specimen measure 4.75 by 3.75 mm. the left having the greatest diameter perpendicularly, while the right has its greatest diameter laterally from the Wolffian duct. The ampullae at this time show a morphology no more complex than at thirty-one weeks, yet resemble to a considerable degree the outline of the distal portion of the vesicles themselves. They have, however, no inner net work of divisions. The common ejaculatory duct formed by the union of the vesicle with the ampulla remains as a rather large dilated structure until well within the substance of the prostate.

SUMMARY

1. During the thirteenth week of intrauterine life the seminal vesicles first appear as lateral evaginations from the walls of the Wolffian ducts in their lower portion just above the tubules of the prostate.

2. By the fourteenth week their future architecture is well outlined with a proximal canal and a branched vesicle proper with definite sacculations.

3. The Wolffian ducts become dilated and their diverticula appear by the nineteenth week.

4. At the twenty-fifth week each vesicle consists of five or more elongated channels which join each other or the proximal canal to form an irregular branching organ.

5. Between the twenty-fifth and thirty-first week is the period of greatest growth.

6. At birth each vesicle consists of ten elongated fingerlike processes with many shallow saccules arising from them. These join each other or the proximal canal to form an extremely irregular convoluted organ. In general both vesicles are similar as regards size and structure, but the details of architecture may vary considerably. They measure at birth 4.75 by 3.75 mm. in diameter.

I desire to thank Dr. Hugh H. Young, Director of the James Buchanan Brady Urological Institute, and Dr. George L. Streeter of the Embryological Department of the Carnegie Foundation for their many courtesies extended during this study.

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PRESENTATION OF CASE HISTORY TO THE LOS
ANGELES CLINICAL AND PATHOLOGICAL
SOCIETY, APRIL 25, 1917

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C. J. H., a fruit broker, aged forty-eight years, first came under my observation April 26, 1914. The following history was obtained. He had had successive attacks of renal colic, the first on the right side in 1908, the second on the left in 1912 and in 1913 two more attacks during which he passed several small calculi. Finally the attack of two weeks duration for which he sought my advice.

Upon abdominal examination the right kidney region was negative: no mass, no tenderness. The left side was the site of a large tumor, very tender to pressure, and roentgenographic examination revealed two large shadows in lower pole. The bladder urine was very cloudy and contained a large amount of pus. Upon cystoscopy the bladder appeared quite healthy. Both ureters were readily catheterized with the following findings: the urine from the right was normal in appearance, slightly acid and negative for pathological elements; the left contained a trace of albumin, a small amount of blood, a little pus and many cells from the convoluted tubules, pelvis and ureter. Phthalein appeared on the right in five and one-half minutes and on the left in four and one-half minutes, the total output for one hour 42 per cent. The badly infected condition of the bladder urine in contradistinction to the specimens obtained by ureteral catheterization could be explained by assuming the existence of two ureters on the left side, the one draining the more healthy half kidney being catheterized.

On May 4, 1914, following an extremely severe attack of colic, the left kidney was exposed and an extensive perinephritis found.

The fatty capsule (of the kidney) was densely adherent to the surrounding structures, including the muscles along the spine and descending colon which were dissected directly from it. The kidney itself was apparently healthy and not involved in the extensive perirenal inflammation. On further examination two distinct cavities filled with granulation tissue, pus and debris were found in the lower portion of the perirenal mass and a definite communication between them and the upper ureter was demonstrated. The infecting organism was the staphylococcus aureus. The fatty capsule was stripped from the surface of the kidney and the multiple abscess cavities removed en masse. It should be stated at this point that two years previously, while cranking an automobile, the patient suffered an injury to the left side which probably explains the origin of the perinephritis.

Following the operation there was considerable nausea and for four days the urine contained a large amount of pus. About three weeks after operation when the wound was almost healed, the patient had a chill and elevation of temperature to 105 followed by anuria. Coincident with this there developed in the right flank a palpable tumor which proved to be the kidney, displaced probably by prolonged straining incident to nausea and vomiting following anesthesia. At operation the ureter was found to be kinked as a result of the ectopic position of the kidney and this apparently resulted in the acute hydronephrosis. After a pyelotomy for drainage had been performed, the kidney was delivered and decapsulated. Beneath the capsule were numerous small abscesses ranging in size from 1 to 5 mm. The kidney was then replaced, many yards of gauze so packed beneath it as to correct the kinked condition of the ureter and a drain sewed into the pelvis. A large catheter passed up the ureter demonstrated its patency. Within a few hours after his recovery from the anaesthetic, a considerable quantity of urine was recovered by the catheter although the bladder had been emptied before operation. The patient improved rapidly, the temperature returned to normal, the urine became clear and the fistula closed. In another three weeks however the ureter again became obstructed, there was urinary retention and fever and a

pyelotomy was done, the resulting fistula persisting until the time of his death.

The patient suffered from severe attacks of pain and was frequently nauseated. During his acute illness he had become accustomed to heroin which controlled the attacks more or less. He led a stormy life of invalidism until March 13, 1917, giving a remarkable exhibition of how a man may live and work under the most unfavorable circumstances. From time to time the ureter would become obstructed, to be followed by chills and elevations of temperature which would confine him to his bed for days, sometimes for weeks.

On October 10, 1916, he complained of pain in the bladder. Upon cystoscopy, the first examination of this kind since the preliminary operation, an ulcer covered by a slough was found on the anterior bladder wall near the position of the air bubble. From this time on the patient's symptoms were referred to the bladder entirely. He bled a great deal and suffered intensely. In January, 1917, under gas oxygen anaesthesia, another cystoscopy served to confirm our former suspicion, namely, that we were dealing with a malignant growth. Catheterization of the left ureter recovered 30 cc. of clear urine free from microscopic pus. There was no obstruction to the passage of the catheter until it reached the apex of the wound in the loin.

His pain continued to increase and on March 8, through an exploratory incision, the bladder was found densely adherent to the pelvis, its anterior and right lateral walls being transformed into a mass with the density of bone. The retroperitoneal glands were enlarged and indurated and the omentum was adherent to the bladder. Death occurred five days later.

At autopsy the findings were of sufficient interest to warrant a detailed description.

The right ureter was 20 cm. in length and dilated; the narrow ureteral orifice readily admitted the passage of a catheter and back of it in the intramural portion of the ureter was a triangular dilatation at the upper end of which was a transverse bar which may have been congenital. Above this for a distance of 5 cm. the ureter was greatly dilated, the area of dilatation however

ending in a definite stricture. At about its mid portion, the ureter is lined by a mucosa much thickened by inflammatory change. The pelvis and calyces were markedly dilated, the calyces containing many cysts ranging in size from 1 to 5 mm. and each of which was filled with a colloid like material. On section the kidney presented a picture typical of interstitial nephritis plus a number of microscopic abscesses. At the lower pole there was scar formation with obliteration of the tubules and glomeruli. On turning back the capsule a most interesting finding was disclosed. A new capsule had been formed, very dense and thick, and new blood vessels could be seen entering it.

On the left side the ureter was markedly dilated and in its lower portion was a moderate sized stone which had disintegrated to a considerable extent. At the time of operation this ureter was palpated as far down as its insertion into the bladder and found to be greatly indurated and thickened.

Examination of the bladder revealed in the region of the trigone, just anterior to the ureteral orifices, ulcers with raised edges. This same condition was found on the floor of the bladder back of the right ureter. On the anterior and lateral walls, extending for some distance into the bladder cavity and diminishing considerably its capacity, was a malignant neoplasm. The symptoms referred to the bladder during the last fifteen months of the patient's life were due to the contracted, ulcerated bladder, the site of a malignant growth.

The most interesting features presented by this case are:

1. It illustrates how little renal tissue is required to preserve human life and to carry on the usual functions of the kidney.
2. The great resistance offered by some individuals to infections of the urinary organs.
3. The reformation of the capsule of the right kidney after its surgical removal by decapsulation.

A COMPARATIVE STUDY OF THE EFFECTS OF THORIUM AND OTHER SUBSTANCES ON THE RENAL PARENCHYMA WHEN RETAINED

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In view of the well recognized damage to the renal parenchyma in pyelography due to the retention of collargol in the renal pelvis, this study was undertaken to determine whether thorium solution ever caused damage to the renal parenchyma when so retained. It was also considered desirable to see what changes might be produced by such innocuous substances as sterile water and normal salt solution, under similar conditions, and also to determine when any parenchymal changes were found, whether or not such changes were due to the retained solution as such or to other concomitant conditions, such as increased intrarenal tension or infection (either introduced or already present).

The pyelographic media selected for study were thorium and collargol because of their more general usage. Since the introduction of thorium solution (1) as a pyelographic medium it has been employed in at least five hundred cases in this clinic with absolutely no untoward effects. Examination of the kidneys which have been removed at operation has failed to reveal any parenchymal change which could be ascribed to the thorium solution used in the pyelographic studies. The dangers due to collargol are well known, whether it be retained or not. Collargol not only acts directly on the kidney itself but in many instances has caused death through its general systemic action. These observations, it will be shown later, have been borne out experimentally. These experiments were controlled by others in which such harmless substances as sterile water and salt solution were introduced into the renal pelvis in the same manner as the pyelographic media. It was also thought well

to see what parenchymal changes would occur in animals where they could be solely due to retained urine as in complete ligation of the ureter.

The procedure used in these experiments was as follows:

After the animal was completely anaesthetized, a skin incision about 4 cm. in length was made beginning in the costo-vertebral angle at the border of the erector spinae muscles and extending along the costal border about 1 cm. below it. After dividing the fascia and muscles by sharp dissection, the lumbar fascia was pierced by a straight clamp, this opening being enlarged by separating the blades of the clamp, and later with the fingers. The posterior parietal layer of the peritoneum was exposed as well as the lower pole of the kidney with its surrounding fatty capsule. The finger was then introduced into the wound and the peritoneum pulled forward. By this procedure the ureter was brought into view lying on the posterior surface of the peritoneum. It was lifted from its bed by a blunt hook and freed from the surrounding tissues by blunt dissection, care being taken not to injure the periureteral vessels. Two heavy silk ligatures were placed around the ureter, the lower one tied tightly and the upper one left loose. The index finger of the left hand was then placed below the ureter and the needle connected by means of rubber tubing with a burette which contained the fluid to be introduced, inserted into the lumen of the ureter. The fluid was allowed to flow into the renal pelvis and ureter by gravity, the burette being held only a few inches above the level of the body of the animal so as to avoid over-distending of the pelvis and forcing the fluid into the renal parenchyma. For this latter reason a syringe was never used in making the injection. After carefully recording the number of cubic centimeters introduced, the upper ligature was tied tightly as the needle was withdrawn. The ureter was then returned to its normal position and the wound closed with silk ligatures throughout. This procedure was employed in twenty-four animals. Of this number in five instances complete ligation of the ureter alone was done. Four had injections of normal salt solution; two injections of sterile water; eight injections of thorium solution; and four injections of collargol.

COMPLETE LIGATION OF ONE URETER

This was done in dogs 1, 17, 18, 23 and 24. In all of these animals hydronephrosis was found at autopsy. In dog 1, at the autopsy sixty-seven days after the ligation, the kidney on this side was found to be smaller than the opposite one (fig. 1). It was greyish in color, and very slight compensatory capsular circulation was present. On section it showed a well marked dilatation of the pelvis and blunting of the calyces, a typical picture of hydronephrosis. Microscopically there was marked fibrosis and pressure atrophy of the tubules, although in some places the latter were dilated and contained hyaline casts. Areas of round cell infiltration were also present. The glomeruli for the most part seemed normal. In other words, the whole picture was one of pressure atrophy. This same microscopic picture was present in all of the kidneys where complete ligation of the ureter was done. The size of the hydronephrotic kidney was apparently influenced very markedly by the amount of compensatory capsular circulation present. This fact has been shown experimentally by Barney (2). In two of the animals, dogs 23 and 24, previous to the ligation of the ureter, the fatty capsule of the kidney was stripped off entirely except at the point of entrance of the renal vessels and ureter into the hilum, thus destroying all collateral circulation temporarily. At autopsy there were numerous adhesions surrounding the kidney operated upon, and the hydronephrosis although present was not so large in these animals as in those where the ureter was ligated and the kidney undisturbed, dogs 17 (fig. 2) and 18, another evidence of the part played by the compensatory circulation in the size of the hydronephrosis. This compensatory capsular circulation of the kidney is best described by Testut (3) and is derived from the following sources; the ureteric, adrenal and spermatic veins, the subcutaneous plexus of the lumbar region and the plexus surrounding the last intercostal, ilio-inguinal and hypogastric nerves. These veins anastomose with the stellate veins of the renal capsule. No renal functional changes were noted in these animals, the phenolsul-

phonphthalein output (two hours) and blood urea content remaining normal throughout the experiment.

In the remaining experiments different substances, water, normal salt, collargol (15 per cent), and thorium (15 per cent) were injected into the renal pelvis according to the above-mentioned method, and ligatures applied above and below the point of injection. All of these animals showed hydronephrosis on the injected side, the largest hydronephrosis being found where salt solution had been injected. Wherever infection was found to be present at autopsy, whether it was already present or introduced at the time of injection, cortical abscesses and pyelonephritis of varying degrees were found. In a great number of these animals distemper was present and while most of them recovered, others succumbed during the course of the experiment.

WATER

Sterile water was injected into the left renal pelvis of dogs 2 and 19, from 1 to 1.3 cc. having been injected. Dog 2 had distemper and an eruption over the entire body. This dog was sacrificed in sixty-seven days. At autopsy a left sided hydronephrosis was found but both kidneys showed a distinct pyelitis. The microscopic picture of this kidney was one of pressure atrophy. Dog 19 sacrificed in forty days showed the same picture of hydronephrosis and pressure atrophy of the cortex on the injected side, but no infection was present. In both instances the hydronephrotic kidney showed a well-marked compensatory capsular circulation.

NORMAL SALT SOLUTION

This was injected into the renal pelvis in animals 3, 11, 13 and 20. The amount introduced varying from 0.85 cc. to 1.3 cc. Of these four dogs no. 3 died in twenty-seven days. At autopsy general peritonitis was due to rupture of an infected hydronephrotic kidney. This kidney was quite large and on palpation yellow pus escaped from a small opening at the upper pole. A well marked compensatory circulation was present.

The cortex was necrotic throughout. The remaining animals were sacrificed in twenty-eight, thirty-five and forty days respectively. At autopsy a large hydronephrosis was found on the injected side with no evidence of infection. These were the largest hydronephroses produced in any of the experiments, the cortex being very markedly thinned and microscopically a typical picture of atrophy was found, the same as presented in dog 1. In these large hydronephroses the compensatory circulation was most marked and seemed to bear out directly the theory that the size of the hydronephrosis was directly proportioned to the amount of compensatory circulation present.

COLLARGOL

A 15 per cent solution of collargol, the same as is used in pyelography was introduced in to the left renal pelvis of dogs 4, 8, 10 and 21. The amounts injected varied from 0.8 cc. to 1.6 cc. Dog 4 died in twenty-three days. There was apparently no decrease in kidney function for the output of phenolsulphonphthalein for two hours was 70 per cent five days before death. At autopsy there was marked pallor of all the tissues and the blood was thin and watery. Grossly the liver showed focal necroses on section. The left kidney showed a moderate degree of hydronephrosis with corresponding atrophy of the cortex. Pyelitis and pyelonephritis were present. Dog 8 died in twenty-six days. There was apparently no decrease in kidney function, the two hour phenolsulphonphthalein output being 62 per cent three days before death. At autopsy the same marked pallor of all the tissues as in the previous dog was noted. Spleen was enlarged, pale and edematous. Liver showed focal necroses. Hemorrhagic enteritis was present. The left kidney showed a moderate grade hydronephrosis, and a fair amount of collateral capsular circulation. On microscopic examination both kidneys showed well marked epithelial and glomerular necrosis (fig. 3). The left kidney showed also some fibrosis and edema. Broncho-pneumonia and central necrosis of the liver were present.

Dog 21 died in eleven days. At autopsy the chief findings were pneumonia and central necrosis of the liver. The left kidney showed a well marked hydronephrosis with compensatory circulation and microscopically, pyelonephritis and pressure atrophy (fig. 4). Dog 10 was sacrificed in twenty-six days. This is the only animal injected with collargol that did not die during the course of the experiment, and this one had the smallest dose, only 0.8 cc. having been injected. The autopsy was entirely negative except for the fact that the left kidney (the injected one) showed a well marked pyonephrosis.

THORIUM

A 15 per cent solution of thorium such as is used in pyelography was injected into the left renal pelvis of dogs 5, 6, 7, 9, 14, 15, 16 and 22. The amounts injected varied from 0.6 cc. to 2.4 cc. Of the eight animals injected two died, no. 5 in four days and no. 6 in twenty days. No. 5 had distemper and diarrhoea and no. 6 had distemper before the injections were made and both showed evidences of it at autopsy. The six remaining animals were sacrificed at intervals varying from twenty-one to fifty-nine days. All showed hydronephrosis of the injected kidney (fig. 5). A well marked compensatory capsular circulation of the hydronephrotic kidneys was found. All of these hydro-nephrotic kidneys showed microscopically the same cortical changes as were seen after simple ligation of the ureter, or after the injection of water or salt solution, namely, pressure atrophy of the cortex, and its attending tubular and interstitial changes (fig. 6). In dogs 9 and 14 there was evidence of infection as shown by the varying degrees of pyelonephritis present. In these animals the examination of the other organs, both gross and microscopical, was entirely negative, showing conclusively that even if thorium solution be retained in the renal pelvis, either permanently as in the case of complete occlusion of the ureter, or for varying periods of time as in partial obstruction of the ureter, it does no systemic damage. These experiments also prove that retention of thorium solution in the renal pelvis

causes no cortical changes whatsoever that cannot be explained entirely by mechanical pressure or the presence of infection. In other words the picture presented by the renal cortex after the injection and retention of thorium solution is absolutely identical with that seen after simple ligation of the ureter or ligation of the ureter after the injection of either sterile water or salt solution. If infection be present the introduction of any solution and its complete retention will invariably cause varying grades of pyelonephritis.

CONCLUSIONS

1. Thorium solution retained in the renal pelvis has no damaging effect whatsoever on the renal parenchyma.

2. Cortical abscesses and pyelitis are due to the presence of infection and not to the retained solution.

3. The cortical changes after the introduction of thorium solution are purely pressure phenomena and are the same as after either simple ligation of the ureter or the introduction of sterile water or normal salt solution into the renal pelvis.

4. Collargol retained in the renal pelvis causes not only great damage to the kidney itself but systemic poisoning most often resulting in death.

5. Ligation of the ureter either alone or after the injection of some solution causes hydronephrosis.

6. The size of the hydronephrosis depends entirely upon the development of the compensatory collateral capsular circulation

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PLATE 1

FIG. 1. Showing the difference in size between the hydronephrotic kidney and the opposite one (Dog 1). The duration of the experiment was sixty-seven days.

FIG. 2. Showing the size of the hydronephrosis and the compensatory capsular circulation (Dog 17). Duration of the experiment was sixty-five days.

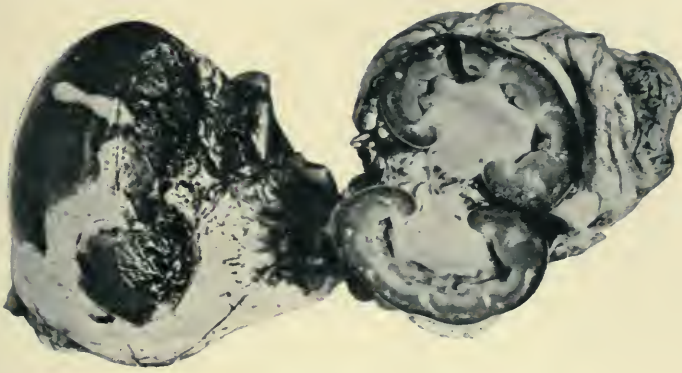


FIG. 1



FIG. 2

PLATE 2

FIG. 3, Photomicrograph of the renal cortex showing extensive tubular and glomerular necrosis due to the retention of collargol in the renal pelvis (Dog 8).

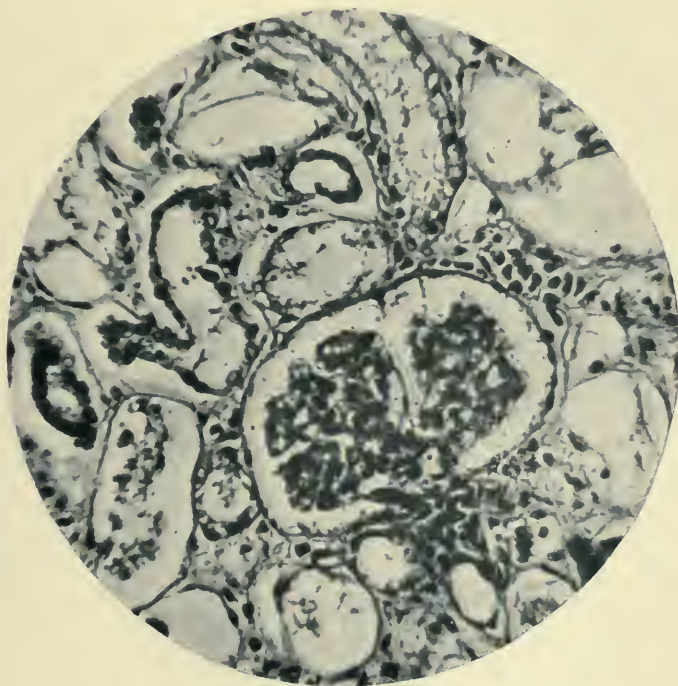


FIG. 3

PLATE 3

FIG. 4. Showing gross cortical changes and hydronephrosis due to the retention of collargol in the renal pelvis (Dog 15).

FIG. 5. Hydronephrosis with no gross cortical changes except pressure atrophy due to the retention of thorium solution in the renal pelvis (Dog 15).



FIG. 4



FIG. 5

PLATE 4

FIG. 6. Photomicrograph of the renal cortex showing no tubular or glomerular changes except pressure atrophy where there is retention of thorium solution (Dog 15).

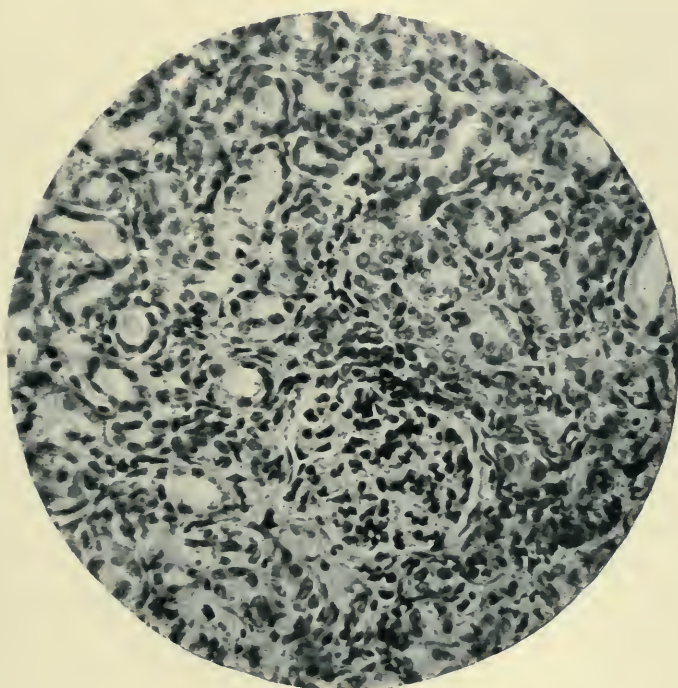


FIG. 6

A STUDY OF PRIMARY HYDRONEPHROSIS

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Legends*

Urologists have long recognised a group of hydronephroses in which no etiological factor was found which would satisfactorily account for the condition. To this group the term "congenital," or perhaps more correctly, "primary" is usually applied. It comprises those cases in which the condition is not secondary to any obstruction demonstrated in the ureter or lower urinary tract. It seems fair to assume that every hydronephrosis is the direct result of some mechanical obstruction to the outflow of urine from the renal pelvis and the object of the present study has been to determine the factors responsible for the development of the condition in the group to which the term "primary" is usually applied.

Considerable attention has been directed in recent years to the rôle played by anomalous blood vessels in the production of hydronephrosis. It has long been recognised that these vascular irregularities are encountered frequently, both in the dissecting room and at autopsy. The surgeon also frequently observes marked variations in the number and course of these vessels associated with hydronephrosis or other pathological processes in the kidney. Quain reports that irregularities in the renal artery are found in about 25 per cent of the cases examined, the most frequent being an accessory vessel arising above or below the normal trunk. Three separate renal arteries on one side were found in about 3 per cent of cases and 4, 5 and even 6 have been observed. A condition of the arterial trunk dividing into multiple branches shortly after it springs from the aorta is sometimes met with and instances of accessory vessels given off from the aorta, inferior mesenteric, spermatic, common iliac

and middle sacral arteries have been reported. The branches of the renal artery or the accessory vessels, instead of entering the kidney at the hilus may penetrate it at the upper or lower pole. In this connection it is with the latter disposition and particularly with the relation of the vessel to the upper ureter that we are chiefly concerned. Thus Mayo in reporting 27 cases of hydronephrosis found anomalous blood vessels in 20 cases, the obstruction in each instance being at a point where the vessel crossed the uretero-pelvic junction. In about 75 per cent of this series of cases the vessel followed a course anterior to the ureter and entered the lower pole of the kidney.

Eckhorn after a study of his own cases and a careful review of the literature concludes that the vessels most frequently productive of obstruction may be divided into two groups: first, those which take a course anterior to the ureter, finally entering the posterior aspect of the kidney in the region of the lower pole; second, those passing behind the ureter and penetrating the anterior surface of the kidney. He states that vessels taking a course anterior or posterior to the ureter and entering the corresponding surface of the kidney, are less frequently productive of obstruction.

Whatever may be the course of the vessel in relation to the ureter, it seems difficult for us to subscribe to the view that it is a frequent primary cause of the obstruction which results in hydronephrosis and we believe that other factors are usually necessary for its production. Movability of the kidney associated with a vascular anomaly may in some cases result in obstruction to the upper ureter or uretero-pelvic junction, particularly when the vessel takes a course posterior to the ureter, but in the majority of cases, the relation of the vessel to the ureter necessary for the production of actual obstruction is, we believe, the result of the altered relations brought about by the increasing size of the pelvis and the descent of the hydronephrotic kidney, caused by a type of obstruction which will be considered later. In some of these cases the vessel at a certain stage of the hydronephrosis may contribute a certain share of the obstruction and in the following case it seems probable that it assumed

this secondary rôle. This patient, aged twenty-four, was admitted October 6, 1915, complaining of infected urine but with no history of any renal pain. He had been operated upon for hernia four years before and had been catheterized on several occasions following operation. Frequent examination of the urine had shown the presence of staphylococcus aureus and upon ureteral catheterization the urine from both kidneys was found



FIG. 1. URETERO-PYELOGRAM SHOWING KINK OF UPPER URETER CAUSED BY ABERRANT BLOOD VESSEL. A LARGE HYDRONEPHROSIS IS ALSO PRESENT

to be infected with the same organism. The total phthalein for the first hour was well over 40 per cent. Pyelography revealed a moderate sized double hydronephrosis, the upper right ureter showing a definite kinking just below the uretero-pelvic junction (see fig. 1). The left uretero-pelvic region was free from any irregularity. The patient was unsuccessfully treated for a long period by pelvic lavage and finally on October 27 1916, the right kidney was explored. The kidney was very

loose and after delivering it a large aberrant vein, emerging from its anterior surface near its lower pole, passed anterior to the uretero-pelvic junction on its way to the vena cava. A moderate hydronephrosis was present, the dilatation beginning sharply at the junction of ureter and pelvis. The kidney sagged considerably and the ureter just beyond its junction with the pelvis was suspended upon the vessel, forming a very considerable kink, as shown in figure 2. The vessel was divided and

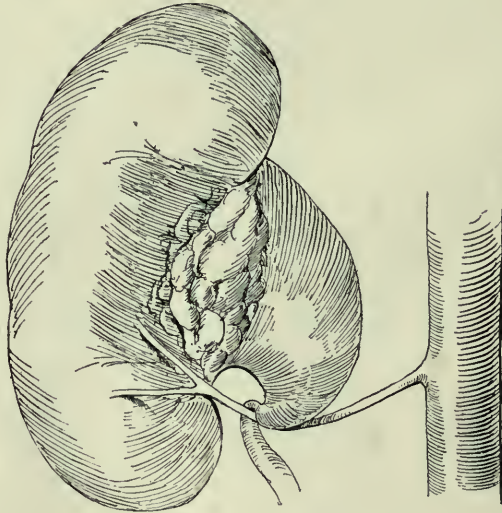


FIG. 2. SKETCH SHOWING THE RELATION OF THE ABERRANT BLOOD VESSEL TO THE UPPER URETER

The ureter just below the uretero-pelvic junction is suspended upon the vessel forming a marked kink.

nothing further attempted, although the operator was not satisfied that the aberrant vessel found was the sole cause of the condition present. A pyelogram taken one month after operation showed some rotation of the kidney and little change in the size of the hydronephrosis but apparently the ureteral kink had been corrected by the division of the vessel. The factors concerned in the development of the hydronephrosis in the opposite kidney were not determined, although the long standing infection may have played an important part in the process.

We would not be understood as saying that vascular anomalies are never the primary cause of hydronephrosis but we are of the opinion that to assign to the anomalous vessel the chief credit for the production of the obstruction is, in the majority of cases, merely the confusion of cause and effect. In support of the view that the anomalous vessel plays a prominent rôle in the production of the obstruction, its advocates cite cases which have been relieved by resection of the vessel. Those who have had occasion to deliver a kidney which has previously been operated upon know how densely adherent it frequently is to the surrounding structures. It seems probable therefore that this postoperative fixation of the kidney plays a most important rôle in the relief of symptoms.

A further argument against the view that the aberrant blood vessel plays so important a rôle in the production of hydronephrosis is the unquestioned frequency of anomalous vessels which pursue a course in intimate relationship with the ureter without producing obstruction. In exposing kidneys which are the seat of other diseases, we have frequently seen vessels occupying positions identical with those described as productive of obstruction, without having occasioned suggestive symptoms or altered the size of the pelvis.

If the blood vessel is ever the cause of the hydronephrosis, the dilatation must begin exactly at the point where the ureter is crossed by the vessel. In looking over many of the illustrations of various articles emphasizing the importance of the vascular anomaly in this connection, it is interesting to note that the hydronephrosis ends considerably above the point where the ureter is crossed by the vessel, the diameter of the ureter between this point and the junction of the ureter with the dilated pelvis being approximately normal or in some instances very slightly dilated. Manifestly if these drawings be correct representations of the actual anatomical relations found, as they purport to be, the blood vessel is not the cause of the hydronephrosis nor has it played any rôle in its production.

RENAL MOBILITY

The frequency of renal mobility associated with hydronephrosis would naturally suggest a very definite causal relationship. Upon this point the views have been widely divergent, some assigning to it a very important rôle, others taking a stand at the opposite extreme.

It is generally supposed that abnormal mobility of the kidney occurs with far greater frequency in women than in men and, as our cases of hydronephrosis have been drawn almost wholly from a male clinic, it is difficult to make deductions from our more or less one sided experience. Certain it is, however, that in our series, there has not been a single instance where the renal mobility could be considered the sole cause of the hydronephrosis. In those cases of renal mobility giving a history of repeated attacks of colic which we have had an opportunity to observe, there has never been a definite hydronephrosis except in those instances in which other factors, coexisting and definitely obstructive, would offer a valid explanation.

It is well in this connection to consider briefly the factors which precede and ultimately lead to the development of hydronephrosis. Experimental investigation as well as clinical observation unquestionably prove that hydronephrosis is the result of an obstruction, either slight or severe, which persists for a considerable period of time and it is not conceivable that the pathological changes of hydronephrosis can be brought about by intermittant distension of the renal pelvis. We do not believe that renal mobility ever brings about an obstruction which is long continued and consequently its uncomplicated presence makes its importance negligible as an etiological factor in the production of hydronephrosis. We have observed many cases presenting histories of intermittant attacks of severe renal colic over long periods in which the modern diagnostic methods failed to reveal any abnormality of the kidney whatsoever. At operation the negative diagnostic findings were confirmed, except for increased mobility associated with fixation of the upper ureter. In none of these cases was there any hydronephrosis, notwith-

standing the fact that the interval obstructions were of long standing. It is interesting to note that simple fixation of the kidney and freeing of the upper ureter was followed in every instance by complete disappearance of the pain.

If renal mobility can produce hydronephrosis, the kinking of the ureter must be assigned as the cause. Kinking of the ureter however does not diminish the size of the lumen because the ureter is not a rigid tube but soft and elastic. It has been shown experimentally, furthermore, that a very acute permanent kink can be produced by suturing the walls of the ureter, without the production of any change in the renal pelvis. In order for a hydronephrosis to develop from an ureteral condition, there must be a reduction in the calibre of the ureter and this is not produced by the kinking.

Abnormally moveable kidney is said to occur in over 20 per cent of women, the combined statistics of seven authorities finding the condition 1049 times in 4576 cases examined. In men however it is supposed to occur in only about 2 per cent or less than one-tenth as frequently as in women. Furthermore, both kidneys are not equally involved, Kelly and Burnam finding it on the right side 177 times in 245 cases. Both kidneys were moveable 43 times and the left alone 25 times. If moveable kidney is the most frequent cause of hydronephrosis, as some authorities contend, we should expect to find, (1) an overwhelming majority of these cases in the female; (2) right hydronephrosis very much more common than to the left; (3) double hydronephrosis to be more frequent than the left alone. Statistics do not confirm this contention.

Why then is moveable kidney assigned as so frequent a cause of hydronephrosis? We believe that it is due in part to the fact that renal mobility is frequently secondary to hydronephrosis; and secondly to a failure to recognise other more potent, although less evident causes of obstruction, occurring either coincidentally with moveable kidney or long preceding it in point of time.

ABNORMAL INSERTIONS OF URETER

At this point it is well to consider briefly a type of ureteral abnormality which is thought by some to represent a congenital defect which plays a definite etiological rôle in the production of hydronephrosis. We refer to the unusual insertions of the ureter into the pelvis, the high and the oblique being the two types most frequently encountered. Normally the ureter enters the pelvis at its lowest point, thus permitting of a complete and easy emptying of the organ. In those instances in which the ureter enters the pelvis at a point considerably above the lowermost portion, it is at once apparent that if the degree of displacement be sufficient, the pelvis will be incompletely emptied.

More careful study of the specimens reported as having these anomalies would probably disclose the fact that these supposed causes of hydronephrosis were in reality the result of the increasing size of the pelvis. When the hydronephrosis increases to considerable dimensions, there is marked sagging of the lower portion of the pelvis, this portion increasing in size more rapidly than the upper. In consequence of this unequal increase in size, the uretero-pelvic junction comes to occupy a relatively high position which at a glance would seem to offer a very definite causal relationship. The altered relations here would seem to be analogous, if not identical, with a condition found in the bladder in cases of obstruction at the vesical neck. As the obstruction increases, the bladder in many cases becomes more and more distended, weakening finally at its most dependent portion and resulting in the formation of the so-called *bas fond*. The development of this condition results in the vesical orifice occupying a relatively very high level and the altered relations would seem to offer a rather apt analogy to the condition found in so many hydronephrotic pelves. With the increase in the size of the hydronephrotic pelvis, there is not only a descensus of the kidney but a swinging inward of its lower portion. These two forces result not only in the high position of the uretero-pelvic junction but explain the valve formation so well shown in the accompanying drawings by Max Broedel (Plate 1).

In case 1 (see plate 2) a high insertion of the ureter is present. Upon superficial examination the ureter apparently entered the pelvis obliquely. A careful study of the ureter however revealed the presence of an extensive fibrosis of its upper portion, the latter factor being the cause of the hydronephrosis. The high implantation and oblique insertion were the effect and not the cause, although as the hydronephrosis increased, it is probable that they played an important, although secondary rôle in its production.

It would seem advisable at this point, before further considering the congenital types of obstruction in the upper ureter, to review briefly the embryology of this structure. It will be recalled that, prior to the development of the kidney in vertebrates, urinary secretion is carried on by structures which subsequently lose this function and in the postfetal stages have no connection whatever with the urinary tract. The earliest of these structures, the pronephros, soon atrophies but its duct persists and forms the excretory canal of the second kidney or, as it is frequently termed, the Wolffian body. At about the fourth week of intrauterine life, there appears upon the dorsal wall of the Wolffian duct near its caudal end, a delicate bulbous epithelial outgrowth which is destined to form the ureter, pelvis and collecting tubules of the permanent kidney. Coincident with the development of the kidney, the Wolffian body and duct lose their connection with the urinary tract, the former developing into the globus major of the epididymis, the latter into the globus minor, vas deferens, the seminal vesicles and ejaculatory ducts.

During the course of ureteral development and persisting for a variable period after birth, marked irregularities in the calibre of the ureter are encountered. Instead of being the relatively smooth and regular canal usually found in the adult, a markedly distorted structure is found. It presents various curves and kinks in its course and instead of its uniformly regular wall, areas of constriction and dilatation are found. Valvules consisting either of plications of the mucosa alone or of the entire ureteral wall are the rule during intrauterine life and in the newborn persist for a variable period in a number of cases. Wolf-

fler in a study of 100 new-borns found 20 more or less well marked transverse folds in the mucosa. As explained by Englisch however, this finding is simply a temporary persistence of the fetal condition and is usually corrected a short time after birth. The factors influencing its correction would seem to be the eccentric pressure of the urine, plus the changes incident to normal development. In a certain number of cases however, due either to the interruption of the normal course of development or to other factors still unexplained, these fetal irregularities persist and may give rise to obstruction resulting in hydronephrosis.

During the past few years considerable attention has been directed to these congenital malformations of the ureter with reference to the rôle they play in the production of hydronephrosis and a large literature has accumulated. We have already considered two anomalies of congenital origin and would further call attention to other usually accepted types of congenital defect. It is customary to include in this list congenital absence and multiplicity of the ureter. Congenital absence of the ureter associated with hydronephrosis, if it ever exist, must be extremely rare. The relatively frequent occurrence of hydronephrosis, associated with multiplicity of the ureter has given this anomaly the credit for actually producing a certain number of these cases. We would call attention to the fact that congenital abnormalities, whether they occur in the ureter or elsewhere are frequently associated with other defects and we believe that when hydronephrosis exists in a kidney with multiple ureters, the hydronephrosis cannot be explained on the basis of ureteral multiplicity but that it has been produced by other concomitant defects which actually produce an obstruction to the outflow of urine. Of these, abnormalities in ureteral calibre are probably the most important and attention will be directed to them later.

We have made a careful study both clinical and pathological of 14 cases of primary hydronephrosis observed within the last few years in the Brady Clinic. We have included in this series only cases in which the obstruction was definitely at the ureteropelvic junction and have omitted cases of calculus, tuberculosis and tumor. In 10 cases the kidney was removed with sufficient

length of ureter to permit of pathological study of the condition present. In 3 cases an exploratory operation was done and plastic procedures carried out for the correction of the obstruction while in 2 cases the diagnosis of primary hydronephrosis was made by means of pyelography and an obstruction at the uretero-pelvic junction demonstrated.

Strictly speaking primary hydronephrosis should include only those cases in which the factor or factors causing the obstruction are not evident. It is generally conceded however that hydronephrosis is, without exception, the direct result of a mechanical obstruction to the outflow of urine from the kidney and, from our experience, we believe that when the dilatation ends sharply at the junction of the ureter and pelvis, and when other agents such as stone, tumor and extrarenal factors are eliminated, a careful search will reveal in the majority of cases one of the types of obstruction we are about to describe.

In our series the obstructions at the uretero-pelvic junction fall into two classes, the congenital and the acquired. Of the former we have found but one case. The remaining cases were all acquired and of inflammatory origin.

CONGENITAL OBSTRUCTIONS

Histologically the ureter resembles the bladder in having three coats, an outer fibrous sheath, a middle muscular layer and an inner mucous coat. The muscular coat consists of inner and outer longitudinal layers and a well developed middle layer of circular muscle. The muscle composing this circular layer constitutes the so-called ring muscles at the site of which there is considerable constriction. These narrow areas are normally present at the uretero-pelvic junction, at the point of crossing the iliac vessels and at the vesical end of the ureter. In rare instances this muscle layer may be considerably hypertrophied, the enlargement constituting a definite obstruction to the outflow of urine which results in hydronephrosis. We have found but one example of this type in our series, a male aged 48, the obstruction in this instance being at the junction of pelvis and

ureter. The symptoms in this case consisted of more or less constant dull aching pain in the right kidney region, extending over a period of years, with outbreaks now and then of quite severe pain, confined to the right lumbar region. On examination the urine was negative for pathological elements and pyelography revealed a large right hydronephrosis. The pathological findings are extremely interesting. As shown in plate 3 the kidney was the seat of a large hydronephrosis while the ureter appeared perfectly normal to its point of entrance into the pelvis. Upon opening the pelvis and ureter, examination revealed a globular enlargement which very considerably encroached upon the orifice. Microscopic section at this point shows a tremendous hypertrophy of the muscle ring as compared with the amount of muscle at this point in the normal. There was no evidence of any inflammation and, aside from the great increase of muscle, no abnormality was found. In this connection it is interesting to note that an analogous condition is occasionally met with in the internal vesical sphincter. This congenital muscle hypertrophy may constitute a very serious obstruction to the emptying of the bladder. Young and Cecil have recently reported such a case.

The rôle formerly assigned to pyogenic infections in the production of ureteral stricture has been almost negligible and it has been customary to consider tuberculosis, trauma and incarcerated calculus as conditions responsible for its development in the vast majority of cases. While strictures of a gross character are seldom found except as a result of the above named conditions, more careful study in recent years has served to show that long standing inflammatory processes may result in the development of infiltrations in the ureteral wall which very considerably narrow its lumen and diminish its elasticity. To Hunner belongs the credit of emphasizing the importance of these lesions and by his accurate methods, he has been able to demonstrate inflammatory infiltrations of the ureteral wall in a large number of cases. His studies have been made almost entirely in the female and he has found an astonishing number of strictures at the level of the broad ligament, although he has detected them

quite frequently at other portions of the canal. Hunner believes that the lesion resulting in ureteral stricture has its primary focus in chronic inflammatory processes often far distant from the urinary tract, as infections of the tonsils, teeth, sinuses, etc. In several of his cases, complete disappearance of symptoms has followed simple dilatations of the strictured area, although in others the condition persisted until the eradication of the diseased focus. His ingenious method of detecting these narrowings consists in the passage of a catheter armed with wax bulbs of varying size through the area of infiltration, upon the withdrawal of which, a sensation is imparted to the hand similar to that occurring as the bougie à boule passes through an area of urethral stricture.

The varying grades of ureteral dilatation and hydronephrosis, as demonstrated by uretero-pyelography in certain cases of long standing pyelitis in which no mechanical obstruction could be found, have usually been ascribed to tissue changes resulting from chronic infection. As Hunner has well brought out, chronic inflammation results rather in a contraction of the tissues involved than in dilatation and it is highly probable that many of the cases of "inflammatory dilatation" are secondary to strictures of the ureter. The presence of an infectious process associated with a bacteruria would, a priori, strongly favor the extension of the inflammation to the adjacent ureter and it is highly probable that narrowing, so slight as to defy detection by the usual diagnostic methods, may explain the resistant character of some of these cases to such therapy as pelvic lavage. Striking indeed are the cases of pyelitis, unfortunately rare, that clear up promptly following the simple passage of a ureteral catheter—a result recalling the response of certain cases of cystitis following the dilatation of urethral stricture.

The mechanical difficulties of employing the method suggested by Hunner with the male cystoscope are considerable and it has not been our experience to detect with certainty many of these ureteral lesions. We feel sure nevertheless that the lesion is an important one to be reckoned with in the types of cases mentioned above, although the marked frequency of ureteral involve-

ment in the region of the broad ligament as described by Hunner, suggests its more frequent occurrence in the female.

In 8 cases of hydronephrosis in which it was considered advisable to do a nephrectomy rather than adopt any plastic procedure, a pathological study of the uretero-pelvic junction has disclosed that in all the cases examined, excepting one, the hydronephrosis was evidently the result of inflammatory narrowing. In practically all of these cases there was slight narrowing at the uretero-pelvic junction noted either at operation or upon examination of the gross specimen after its removal. The true nature of the obstruction was only revealed however by careful microscopic study of this region, which brings out the fact that many of these strictures are very slight, there being no bridle or obstruction projecting into the lumen, a narrowing simply being present. In this connection we desire to emphasize the danger of mistaking an old inflammatory lesion for a congenital one. Cases 3 and 5 illustrate this point extremely well and, after superficial examination of the sections, we classified them with those of congenital origin. In long standing inflammatory processes, the mucous membrane may be intact and the only gross change is a marked narrowing of the upper ureter. In some instances the area of constriction is very short involving the ureter for a distance of only a few millimeters; in others the upper 2 or 3 cm. of the ureter may be the site of a spindle shaped contraction, the ureter at this point measuring from one-third to one-half the diameter of the portion immediately below. In the latter type, the constriction is perfectly evident at operation although the cases having a short constriction may be difficult of detection upon external examination. If upon microscopic examination, the mucous membrane appear intact, while beneath it a marked increase in fibrous tissue be present, in the absence of any inflammatory elements, one might readily diagnose the condition as a congenital one. We would point out however that in all inflammatory processes, the end point is a fibrosis, the examination of which may disclose nothing to suggest its former inflammatory nature. In the two cases cited above, there was a marked increase of connective tissue just beneath the mucosa

and only after a very careful examination were a few areas of round celled infiltration found, thus proving its inflammatory origin.

In 10 cases of this series in which nephrectomies were done the urine was sterile and this makes it all the more probable that the inflammatory process found in the ureteral wall, causing a diminution in its calibre and loss of elasticity, was the etiological factor. The finding of an inflammatory infiltration, associated with a gross urinary infection however, would not prove conclusively that the ureteral wall lesion was the cause of the hydronephrosis. In only 3 cases, upon incision of the uretero-pelvic junction and without a microscopic study, could we be certain as to the character of the lesion. In all the remaining cases, microscopic study of the tissue was necessary to demonstrate the presence of an inflammatory process. As has been remarked above, marked contraction of the ureter is not necessary in order to obstruct the outflow of urine from the pelvis. It is well known that a contraction in the lower portion of the ureter may cause very slight, if any, hydronephrosis, whereas if this same degree of contraction be present at the uretero-pelvic junction, a marked and rapidly developing hydronephrosis will result. The reason for this is obvious. The ureter being a strong muscular tube can overcome a considerable degree of obstruction before any marked dilatation develops and when this dilatation does begin above the point of obstruction, it travels slowly upward. The kidney is therefore protected from back pressure until the entire ureter as far as the renal pelvis is dilated. An exact analogy of the behavior of the ureter under such conditions is to be found in urethral stricture. It is a matter of common knowledge that marked contraction of the pendulous urethra may exist without producing partial or complete retention, although the size of the stream may be considerably diminished. This same degree of contraction, if present in the bulb, will more quickly cause severe urinary difficulty, while contractions at the vesical orifice, long before the calibre is greatly diminished, may result in complete retention. The urethra is a powerful muscular tube and its propelling force, added to that of the bladder, can

overcome a degree of obstruction which the bladder alone is unable to accomplish.

An unusual example of ureteral stricture which suggests an interesting problem in the physiology of the ureter is shown in fig. 3. The patient, a male, aged forty-six, was admitted Janu-

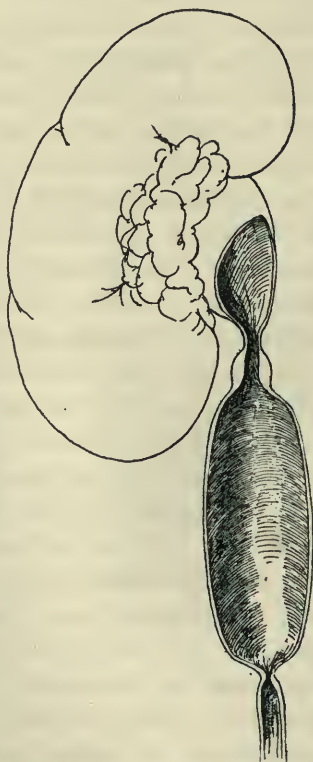


FIG. 3. INTERESTING CASE OF TWO STRICTURES OF THE URETER SEPARATED BY MARKED HYDROURETER

The diameter of the ureteral lumen at the upper stricture is diminished and there is only slight dilatation of the upper ureter and pelvis.

ary 29, 1918, with the history of marked urinary frequency for three years. From time to time there was slight hematuria but there had never been any symptoms referable to either kidney. Examination upon admission revealed a wide calibre stricture

of the bulbous urethra which prevented the passage of the cystoscope. The urine was very cloudy from pus and colon bacilli. After dilatation of the stricture, cystoscopy found 75 cc. of residual urine and a bladder capacity upon forced distension of only 140 cc. Upon ureteral catheterization the left catheter passed readily but the right met an obstruction which prevented its introduction. The urine from the left side was infected although the output of phthalein in one-half hour was 35 per cent. The transvesical phthalein was zero. At operation on February 27 the kidney and most of the ureter were removed.

Examination of the specimen shows a kidney which is only slightly hydronephrotic. The upper end of the ureter is not dilated but about 2 cm. below the kidney there is present a marked stricture. The wall of the ureter at this point is very greatly thickened but the calibre of its lumen is only slightly diminished. Immediately below this dense stricture, the ureter is enormously dilated for a distance of 12 cm, the lumen approximating that of the small intestine in size. Immediately below this the ureter presents another stricture of filiform diameter which involves the ureter for only a short distance. The remainder of the ureter is apparently normal. The point of interest is that, in the presence of these two dense strictures and with an enormous degree of hydroureter, the upper segment of the ureter is only slightly dilated and there is present only a slight grade of hydronephrosis. Both strictures are apparently of about the same duration and the obstruction produced by the lower stricture resulted in the enormous dilatation of the ureter. The great increase in the intraureteral pressure at this point prevented the permanent contraction of the upper stricture, the resistance of whose fibrous wall in which there is a great deal of hypertrophied muscle, served as a protecting barrier to the ureter and kidney above.

In the following cases of hydronephrosis nephrectomies were done and a sufficient portion of the upper ureter removed to permit of microscopic study of the uretero-pelvic junction. In all of the cases examined an inflammatory lesion at the junction of the pelvis and ureter was demonstrated.

Case 1. Male, aged twenty-nine. Admitted November 29, 1915, with the complaint of pain in the right side. His health had always been good and, except for an attack of gonorrhoea of six weeks duration three years prior to the onset of his present illness, his personal history was negative. The condition for which he consulted us was of insidious onset, beginning about four years before admission. The patient was conscious of a constant, dull ache in the region of the right kidney which did not become acute until April, 1915. At this time it gradually became worse and for a period of ten days he suffered from more or less constant severe pain located in the right abdomen and back. During this time there was high fever and the urine which was previously clear now contained a large amount of pus, blood and albumin. From this time on the patient was conscious of the presence of a large tumor mass in the right abdomen. Following the subsidence of the first attack, he was free from serious pain until two weeks before admission when he suffered another attack similar to the first. This attack lasted for twelve days, there was high fever and the urinary findings were identical with those accompanying the first attack.

Examination. In the right upper abdomen there was visible a large rounded swelling which became considerably more pronounced when the patient assumed an erect posture. Palpation revealed a mass, rounded, smooth, hard, somewhat larger than a croquet ball and not tender to pressure. It descended slightly with inspiration and permitted of slight movement with the hand. The bladder urine was negative for pathological elements and the total phthalein for one hour was 50 per cent. Upon cystoscopy the bladder appeared perfectly normal. Both ureters were catheterized, the urine from the left side being normal and the output of phthalein for one-half hour being 35 per cent. No urine could be recovered from the right catheter. Plain x-rays of both kidneys revealed no suggestive shadows and a pyelogram of the right was unsuccessful, owing to the fact that fluid could not be introduced into the renal pelvis. The pyelogram of the left kidney was normal.

Operation. A very large right pyonephrosis was removed through a right lumbar incision. The specimen was interesting in that it presented two anomalies, the one congenital, the other acquired. It consisted of a large pyonephrotic sac containing practically no renal tissue except at the upper pole where a portion of parenchyma 9 by 4 by 3 cm. was found. Upon further examination two ureters were discovered, the upper one draining the remaining and apparently normal por-

tion of kidney, the other entering the pyonephrosis at a point above and internal to the lower pole. The upper ureter was normal and its pelvis showed no dilatation. The lower ureter however for a distance of 2 inches below its junction with the pelvis was fibrous, with practically complete obliteration of the lumen.

Case 2. Male, aged twenty-nine. Admitted November 14, 1916, with the history of dull, aching pain in the left kidney region associated with urinary frequency. The condition had begun eighteen months before. At no time had the pain been severe and had been characterized throughout by an aching sensation and a feeling of distension in the left hypochondrium.

Examination. Upon abdominal examination neither kidney was palpable. Except for some tenderness upon pressure over the left kidney region, nothing definite was made out. Examination of the bladder urine revealed many pus cells and a large number of colon bacilli. The total output of phthalein for one hour was 41 per cent. Upon ureteral catheterization no. 7 catheters were readily introduced into the renal pelves. The urine from the right kidney was normal and the output of phthalein for one-half hour was 26 per cent. The left urine contained pus and many colon bacilli and no phthalein was secreted in one-half hour.

Operation. A left nephrectomy was done. The kidney is a little larger than normal, very thin walled and of no functional value. The pelvis is dilated to three or four times its normal size and at the exact point where the dilatation of the pelvis ends there is a definite narrowing of the ureter. The ureter at this point is considerably smaller than the portion below and the constriction measures about 2 cm. in length. Upon section the lumen is very tortuous, irregular and greatly narrowed by scar. Microscopically the mucosa is intact but beneath it there is a great increase of fibrous tissue which has replaced largely the submucous and muscle layers. Scattered here and there are collections of round cells.

Case 3. Male, aged twenty-two. Admitted December 14, 1915, with the complaint of pain in the left lower abdomen. Two and one-half years before he had suffered from a severe attack of pain, beginning in the lower left abdomen and radiating to the right of the midline. This attack lasted twenty minutes, during which time he had marked urgency of urination. He continued to have some urinary frequency and two months later had another attack requiring a hypodermic of morphia. Since this time he has suffered from repeated attacks of

pain which have increased in severity and duration. At no time has the pain radiated into the testicle and there has been no hematuria or passage of calculus.

Examination. Upon ureteral catheterization the urines from each side were negative for pathological elements. Thirty-five per cent of phthalein was secreted from the right kidney in one-half hour but only a faint trace was recovered from the left. The x-ray examination



FIG. 4. URETERO-PYELOGRAM SHOWING LARGE HYDRONEPHROSIS AND STRICTURE OF THE UPPER URETER

of the left kidney revealed a very interesting condition. The kidney was quite low extending to within 1 inch of the iliac crest. In the region of the lower pole were three groups of shadows cast by many small seed calculi. The kidney was the seat of an extensive hydronephrosis, the dilatation ending sharply with the beginning of the ureter. The ureter for a distance of 1.5 cm. below the pelvis was very narrow, containing but a trace of collargol. The remainder of the ureter was of normal size (see fig. 4).

Operation. Upon delivering the kidney it was found to be dilated and soft, particularly at the lower pole. The extra-renal portion of the pelvis was rounded and small, being about the size of a golf ball. Just at the junction of the pelvis and ureter, there was a definite constriction which apparently caused considerable obstruction as the pelvis was still distended with urine after the manipulation required to free the kidney. A small incision was made through the uretero-pelvic junction and immediately urine containing a large number of small seed calculi escaped. The extensive destruction of the kidney, together with the presence of the large number of seed calculi made a plastic operation inadvisable and the kidney was removed.

Upon examination of the specimen the pelvis and adjacent ureter are extremely thin. The mucosa has been replaced in large part by fibrous tissue and this fibrosis extends well into the muscle layers. There is also an extensive infiltration of round cells.

Case 4. Male, aged forty-four. Admitted December 5, 1916, with the history of repeated attacks of pain since 1898. Frequent examinations of the urine since this time have always revealed the presence of a large amount of pus.

Examination. Urinalysis at the time of admission revealed a marked pyuria with colon bacillus infection. Upon ureteral catheterization the urine from the right kidney contained the same infection and the output of phthalein for one-half hour was nil; the left urine was normal and the phthalein output 30 per cent. Pyelography revealed a large hydronephrosis, the dilatation of the pelvis ending sharply at its junction with the ureter. The ureteral outline was normal.

Operation. Upon delivering the kidney a marked grade of destruction was found. The pelvis was enormously dilated to the point where the ureter entered it. At the junction of ureter and pelvis there was a slight kink and the ureter at this point was considerably narrower than the portion immediately below. The kidney was removed.

On opening the pelvis and ureter an extremely interesting condition was found. As shown in plate 4 the junction of pelvis and ureter there is present a bar of tissue which extends transversely across the lumen greatly obstructing the outlet. The bar was elevated above the floor of the adjacent ureter for a distance of 2 or 3 mm. and behind it on the pelvic side was a considerable depression. The whole picture reminded one strongly of some of the inflammatory contractures seen at the vesical orifice. Microscopic examination of the tissue revealed an unmistakable picture of chronic inflammation.

Case 5. Male, aged thirty-seven. This patient was admitted August 15, 1916, with the history of intermittent attacks of left lumbar pain for the preceding eight months. The pain usually came on gradually, was of dull, aching character and remained confined to the left lumbar region beneath the costal margin. Its duration varied from two hours to three days.

Examination. Abdominal examination revealed no areas of tenderness. Both kidneys were just palpable at their lower poles, smooth



FIG. 5. DOUBLE URETERO-PEYLOGRAM SHOWING A NORMAL CONDITION ON THE RIGHT AND HYDRONEPHROSIS WITH STRICTURE AT THE URETERO-PELVIC JUNCTION ON THE LEFT

and not painful to pressure. The urine was negative both chemically and microscopically and the total output of phthalein for one hour was 40 per cent. Upon ureteral catheterization the urine from the right was of normal color, that from the left being very pale. The phthalein test was not satisfactory owing to inhibition of function. As shown in figure 5, pyelography revealed a large hydronephrosis with a very definite narrowing at the uretero-pelvic junction.

Operation. The renal pelvis was quite prominent and even when

considerable pressure was made it remained distended with urine. The kidney with a portion of adjacent ureter was removed.

As shown in plate 5 the pelvic dilatation ends sharply with its junction with the ureter. The ureter for a distance of 2 cm. below this point is narrow and spindle like, being about half the diameter of the normal ureter. We were at first of the opinion that the narrowing was one of congenital origin and it was not until a careful microscopic study of the tissue was made that its inflammatory character was proved. While the epithelium was intact the tissues beneath consisted almost wholly of scar, the fibrosis extending deeply into the muscle.

Case 6. Male, aged twenty-five. There was a history in this case of intermittent attacks of left sided pain for many years. The pain was confined to the left abdomen beneath the costal margin and did not radiate. There was no history of the passage of a calculus or hematuria.

Examination. Upon examination the urine was normal and ureteral catheterization found a functionless kidney on the left. Pyelography revealed an enormous hydronephrosis, the dilatation beginning exactly at the junction of the pelvis and ureter.

Operation. At operation an extreme narrowing was noted at the uretero-pelvic junction and the kidney was removed. Unfortunately the specimen was lost and a histological study could not be made.

Case 7. Male, aged twenty-eight. This patient was admitted June 22, 1916, with the history of intermittent attacks of pain for seven months. The pain was always located beneath the right costal margin and was unassociated with hematuria of the passage of calculus.

Examination. Upon examination the bladder urine was sterile and the total phthalein 55 per cent for one hour. Upon ureteral catheterization no urine could be obtained from the right catheter. The urine from the left was normal and the one-half hour phthalein 40 per cent. As shown by pyelography, the right kidney is the seat of a large hydronephrosis.

Operation. On exposing the kidney a large sacculated hydronephrosis was found, the dilatation of the pelvis ending abruptly with the upper ureter. There were no abnormal blood vessels and the pelvis was negative for stone. The kidney was completely destroyed and an nephrectomy was done.

On opening the pelvis and ureter, an obstruction which resulted in the hydronephrosis was found in the upper ureter. As shown in plate 6, the ureteral lumen is very tortuous and markedly contracted by

scar. Microscopic examination of the tissue shows an almost complete replacement of the normal structures by inflammatory elements.

Case 8. Male, aged twenty-four. The symptoms in this case began six months before admission when the patient suffered from a severe attack of pain confined to the region of the left kidney. Since the onset of the illness, there had been 6 attacks of pain, the average duration of each being from two to three days. The pain was unaccompanied by any other symptoms.

Examination. Ureteral catheterization revealed the absence of infection in either kidney and the one-half hour phthalein output from the right was 30 per cent as against 12 per cent on the left. A left hydronephrosis was demonstrated by pyelography.

Operation. Upon exposing the left kidney a very large extrarenal pelvis of 50 cc. capacity was found. The upper ureter appeared normal except for a definite narrowing just at its point of junction with the pelvis. The obstruction was considerable apparently as the manipulation required to free the kidney, failed to empty its urinary contents. Upon opening the pelvis and ureter, the uretero-pelvic junction was greatly constricted and the microscopic picture was similar to that noted in case 3.

Case 9. Male, aged twenty-three. Admitted January 10, 1914. During the three years prior to his admission, he had suffered from frequent attacks of pain in the region of the right kidney. This was his sole symptom.

Examination. The urine was free from pathological elements and the total phthalein 50 per cent. Upon ureteral catheterization a sterile but functionless kidney was found on the right and pyelography revealed a large hydronephrosis, the dilatation ending abruptly with the beginning of the ureter.

Operation. An enormous hydronephrosis was removed. Study of the junction of ureter and pelvis showed some narrowing in the gross and on microscopic section a picture typical of chronic inflammation was found.

The following are cases in which plastic operations were done and no tissue could be obtained for microscopic study. The hydronephrosis however was apparently the result of obstruction in the uretero-pelvic region and they are most probably of a type similar to those noted above.

Case 1. Male, aged nineteen. Admitted January 30, 1917, with the complaint of pain in the left lumbar region. This symptom had begun six years before, since which time the patient had suffered from intermittent attacks of dull, aching pain. The pain was never very severe or lancinating in character, did not radiate and was usually of about two hours duration.

Examination. Abdominal examination was entirely negative, there being no masses or areas of tenderness. The bladder urine was clear, free of albumin, casts and infection but upon centrifuging a number of red blood cells were found. Repeated total phthaleins showed an output of from 14 to 26 per cent for the first hour and 33 to 42 per cent for the second hour. Upon cystoscopy the bladder was perfectly normal. Ureteral catheterization showed an output of phthalein of 20 per cent from the left kidney in one-half hour but none was recovered from the right and the bladder contents failed to show any trace of the dye. Pyelograms of both kidneys show a large double hydronephrosis. The right kidney is apparently completely destroyed while on the left the destruction is not so far advanced. The outlines of the ureter and uretero-pelvic junction on the right are indistinct but on the left the entire ureter appears normal.

Operation. At operation on January 31, 1917, the left kidney was exposed through a lumbar incision. Examination revealed a greatly enlarged extrarenal pelvis and for a distance of 0.75 cm. below the uretero-pelvic junction a distinct narrowing of the ureter, the ureter below this point being of normal size. Three tension sutures were now taken; one at the junction of the ureter and pelvis, one at a point about 1.5 cm. from the uretero-pelvic junction in the pelvis of the kidney toward the lower pole, the third 1.5 cm. below the junction on the outer surface of the ureter. A horse-shoe shaped incision was now made through the ureter and pelvis connecting these three points. The incision was now treated in a manner suggesting the pyloroplasty of Finney. The inner edges of the pelvic and ureteral limbs of the incision were approximated by a continuous suture of fine catgut following which the outer limbs of the incision were brought together in a similar manner. The fatty capsule was then placed around the region of the plastic and a tube drain carried down behind the kidney.

The convalescence from operation was uneventful. There was no urinary drainage from the wound and the patient was discharged from the hospital in three weeks. When seen one year later, he had been entirely free from symptoms and had had no recurrence of the attacks of pain.

Case 2. Male, aged thirty-two. Admitted August 10, 1915, with the complaint of pain in the left side. Fifteen years before the patient had had several attacks of pain in the left kidney region. The attacks would begin suddenly and were usually precipitated by violent exercise. During the past thirteen years the patient has suffered annually from 3 to 4 attacks of pain. The pain is usually dull, aching in character, remains confined more or less to the left upper abdomen and gradually disappears in the course of two or three hours. The attacks

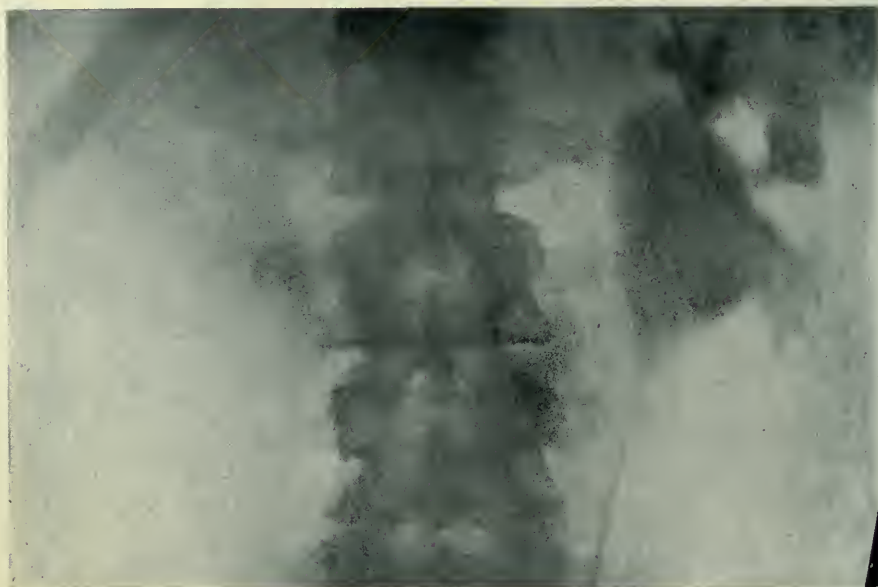


FIG. 6. PYELOGRAM SHOWING LARGE HYDRONEPHROSIS, THE PELVIC DILATATION ENDING SHARPLY AT THE BEGINNING OF THE URETER

have frequently been associated with nausea and vomiting and in recent years hypodermics of morphia have been necessary.

Examination. Pyelography revealed an enormous hydronephrosis on the right side while the left kidney showed a similar process to a lesser degree. The ureters were free from any irregularity and the dilatation ended exactly at the junction of pelvis and ureter (see fig. 6).

Operation. Upon exposure of the left kidney, it was found to be twice the size of normal, of good color and rather firm. The pelvis was extrarenal and apparently almost all of the hydronephrosis was

confined to it. The manipulation of freeing the kidney and ureter failed to empty the 100 cc. of urine it contained and as the dilatation commenced sharply at the junction of the pelvis and ureter, the obstruction was thought to be at this point, although there was no external evidence of any stricture. An incision 0.75 cm. in length, made through the long axis of the ureter and pelvis at their point of junction, revealed a very definite narrowing. The obstruction was corrected by the application of the Heineke-Miculicz principle, the two poles of the incision being approximated by catgut suture. Since operation the patient has had no recurrence of the attacks of pain.

Case 3. Male, aged twenty. For three years prior to his admission on April 16, 1914, this patient had suffered from intermittent attacks of pain in the left side, the pain being located just above the crest of the ilium in the axillary line.

Examination. Upon examination of the abdomen no abnormalities were found. The bladder urine was uninfected and the output of phthalein for one hour was 55 per cent. Pyelography revealed a large hydronephrosis, the dilatation ending at the junction of pelvis and ureter.

Operation. At operation the kidney appeared normal except for fetal lobulations. The pelvis was greatly dilated and a marked constriction was found just at the junction of the ureter and pelvis. There was no dilatation of the ureter below this point, its upper portion was not fixed and no abnormal vessels were found. No calculus was found in the pelvis or calyces. An incision was made in the lower portion of the pelvis and carried down into the ureter through the constricted junction and sutured together in the opposite direction.

DIAGNOSIS

With our modern methods the diagnosis of hydronephrosis is comparatively easy. The demonstration of the cause of a given hydronephrosis however may offer considerable difficulty and in a certain number of cases it must be made by elimination. If the pelvic dilatation ends sharply at its junction with the ureter and if the ureter shows no evidence of obstruction lower down, it is reasonable to assume that the obstruction lies at the point of junction of the pelvis and ureter. In certain instances a definite narrowing of the upper ureter may be demonstrated by

uretero-pyelography and in cases where an aberrant blood vessel plays a rôle in the obstruction, a kink in the upper ureter may be found. We have been able to demonstrate the former condition in two cases and the latter in one. In other cases however the diagnosis can be made only by eliminating calculus, tuberculosis and tumor. In some cases, upon exposing the pelvis and ureter, the area of stricture can be determined by external examination, while in others an incision through the uretero-pelvic junction is necessary to demonstrate it. In our series of cases we have found but one which was of congenital origin and we believe that this type of obstruction in this region must be extremely rare. Before making a careful histological study of these specimens, however, we had considered many of them congenital. We desire therefore to emphasize the fact that the narrowings occurring at the uretero-pelvic junction are usually secondary to inflammatory processes.

The method of Hunner will no doubt facilitate the recognition of a certain number of these cases in the female, particularly those in which there is a considerable area of scar. In others in which the narrowing is slight and the mucosa intact, it may be difficult to distinguish a lesion from the ring muscle. As has been indicated above, the application of Hunner's method in the male will not be successful in many cases. The water cystoscope when used for ureteral catheterization has as its chief shortcoming the difficulty of overcoming slight obstructions, such as may be occasioned by an unusual course of the ureter through the bladder wall, ureteral kinks or the catching of the catheter tip in the folds of ureteral mucosa. In order to detect a stricture with the wax bulb, it is of course first necessary to pass it through the area of narrowing and upon its withdrawal the characteristic "hang" is obtained and the diagnosis made. Unquestionably a large majority of these narrowings if sufficient to cause hydro-nephrosis will prevent the passage of the wax bulb and we believe that the application of this method in the male will be of slight aid to diagnosis.

TREATMENT

The recognition that so many of these cases of so-called primary hydronephrosis are due to inflammatory contracture naturally suggests the possibility of employing dilatation as a means of relieving the obstruction. Unfortunately in the vast majority of cases the process is so far advanced and the obstruction of such long standing that attempts at dilatation seem hardly warranted. Especially is this true when the kidney is converted into a pus sac or when its functional value has been practically destroyed and intense symptoms of distress are present. Again when the inflammatory process is of long duration and when a large amount of fibrous tissue is present, dilatation if secured, will only result in temporary relief because of subsequent contraction. There is a possibility that if these cases could be secured before the development of a large amount of scar tissue in the ureteral wall that dilatation might prove of considerable value.

So far as the operative treatment of a given case is concerned, it would seem to make little difference whether or not the stricture was of the acquired or congenital variety. The determination of the presence or absence of infection in the urine from each side together with the functional value of each kidney will be of great aid to the selection of the proper operative treatment. If a bilateral hydronephrosis be present, with a reduction in the total functional capacity of the kidneys, procedures designed to correct the obstruction are infinitely preferable to nephrectomy. In other cases in which the hydronephrosis is slight, but apparently progressive, and in which the condition is not complicated with infection, the conservative plastic operation is certainly the method of choice. On the other hand a marked grade of infected hydronephrosis with full compensation established in the opposite kidney would call for nephrectomy.

The nature of the operative treatment therefore will depend upon several factors. As hydronephrosis is more often unilateral and as the majority of cases is infected, nephrectomy is the operation most frequently employed. There is however a

certain number of cases in which nephrectomy is distinctly contraindicated and in which it may be possible by a plastic operation to remove the obstruction, thus relieving the patient's symptoms and preventing further progression of the disease. The plan of procedure will vary somewhat with the character and extent of the stricture. If the narrowing does not involve the ureteral wall deeply or for an extent exceeding 0.5 cm., the Heineke-Miculicz principle may be successfully employed (see plate 7). The pelvis and upper ureter having been well freed, an incision beginning at a point a few millimeters on the pelvic side of the junction of the pelvis and ureter is carried through all the coats of the posterior wall to a point a few millimeters on the ureteral side of the stricture. The poles of the incision are now approximated so that, whereas the long axis of the incision was formerly vertical, it is now more or less horizontal. Fine catgut should be used in making the approximation and if possible the suture should not include the mucosa. The fatty capsule is wrapped about the operative site and a rubber tube and cigarette drain are carried down behind the kidney to within a short distance of the ureteral wound.

In cases in which the stricture involves the upper ureter for a distance exceeding 1 cm., the Heineke-Miculicz principle is not applicable and one of two procedures may be employed. If the upper ureter is the seat of an extensive fibrosis which destroys its pliability and renders a plastic operation difficult, the better course to follow is the one shown in plate 8. This consists in the amputation of the ureter below the area of stricture and the anastomosis of the free end into the renal pelvis. This method is so well shown in the accompanying illustration as to render further description unnecessary.

In other instances in which the upper ureter, although narrowed for a considerable distance is not so rigid as to require its amputation, a third method may be employed. This method recalls the pyloroplasty of Finney and the various steps in the procedure are well shown in plate 9. After thoroughly freeing the kidney and upper ureter, an incision beginning at the lowermost portion of the strictured area is continued in horse-shoe

fashion around through the adjacent pelvis to a point corresponding to the lower level of the ureteral limb. The medial edges of this incision are approximated with fine catgut, thus forming the floor of the future canal. The lateral edges of the incision are then brought together in a similar manner and the procedure is completed. A six to eight day catgut should be used and as the suture includes the mucosa, care should be taken to tie the knots externally. The site of the plastic is now covered with the fatty capsule. Because of the contamination of the wound with urine which is frequently infected and the further possibility of temporary urinary leakage, a rubber tube and cigarette drain should be carried down to the vicinity of the plastic.

CONCLUSIONS

The study of our material shows that the most frequent cause of so-called primary hydronephrosis is an inflammatory contraction at the uretero-pelvic junction, and we believe that more careful microscopic study of this region in cases of hydronephrosis, without apparent cause, will disclose this lesion in a large percentage of them. In many cases in which aberrant blood vessels, renal mobility, or abnormal implantation of the ureter have been assigned as the cause of the hydronephrosis, careful examination of the upper ureter and pelvis will reveal inflammatory narrowings which have unquestionably played the primary rôle. When the kidney is extensively destroyed, nephrectomy, if not contraindicated, should be carried out. When the kidney, however, possesses valuable renal function or when a bilateral condition contraindicates nephrectomy, the various plastic procedures outlined above offer considerable prospect of success.

PLATE 1

SERIES OF FIVE DRAWINGS SHOWING THE DEVELOPMENT OF HYDRONEPHROSIS

As the kidney descends it swings over toward the midline as shown by the arrows. With the descensus and swinging inward there is a corresponding elevation of the uretero-pelvic junction resulting in valve formation which increases the obstruction (Kelly and Burnam).

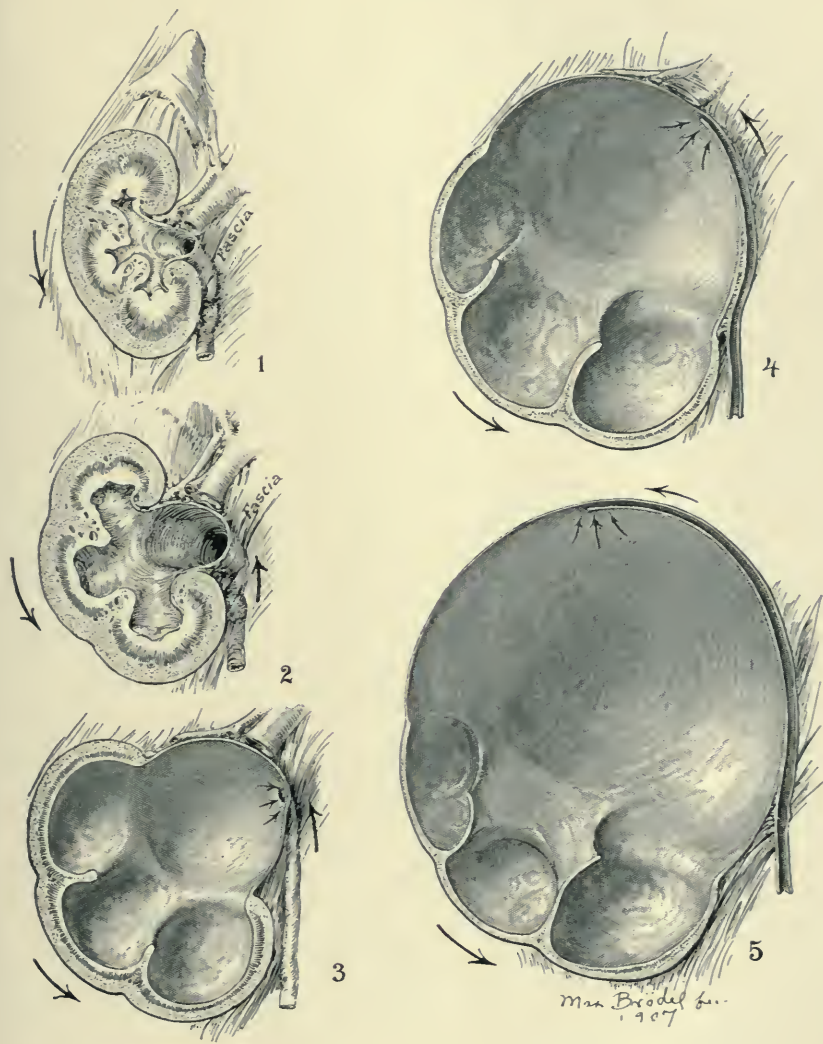


PLATE 2

ANTERIOR VIEW OF DOUBLE KIDNEY, THE LOWER HALF OF WHICH IS HYDRONEPHROTIC

The pelvis and ureter of the upper half are normal. The upper portion of the lower ureter is fibrous throughout and enters the posterior wall of the pelvis just below its mid portion.



PLATE 3

SHOWING LARGE HYDRONEPHROSIS CAUSED BY CONGENITAL DEFECT AT THE
JUNCTION OF PELVIS AND URETER

The insert shows a globular enlargement obstructing the ureteral orifice. Microscopic study of this area showed it to consist entirely of smooth muscle and the condition represents no doubt a congenital hypertrophy of the ring muscle.

PRIMARY HYDRONEPHROSIS

JOHN T. GERAGHTY AND WILLIAM A. FRONTZ

PLATE 3



PLATE 4

LARGE HYDRONEPHROSIS CAUSED BY INFLAMMATORY STRICTURE AT THE
URETERO-PELVIC JUNCTION



PLATE 5

SHOWING MODERATE SIZED HYDRONEPHROSIS CAUSED BY SPINDLE SHAPED
CONTRACTION OF THE UPPER URETER

PRIMARY HYDRONEPHROSIS

JOHN T. GERAGHTY AND WILLIAM A. FRONTZ

PLATE 5



PLATE 6

LARGE HYDRONEPHROSIS SECONDARY TO INFLAMMATORY STRICTURE OF THE
UPPER URETER

The insert shows the great narrowing and tortuosity of the ureteral lumen.



PLATE 7

THE PLASTIC SHOWN INSURES A WIDENING OF THE URETERO-PELVIC
JUNCTION WHEN THE STRICTURE INVOLVES THE URETER FOR ONLY
A SHORT DISTANCE

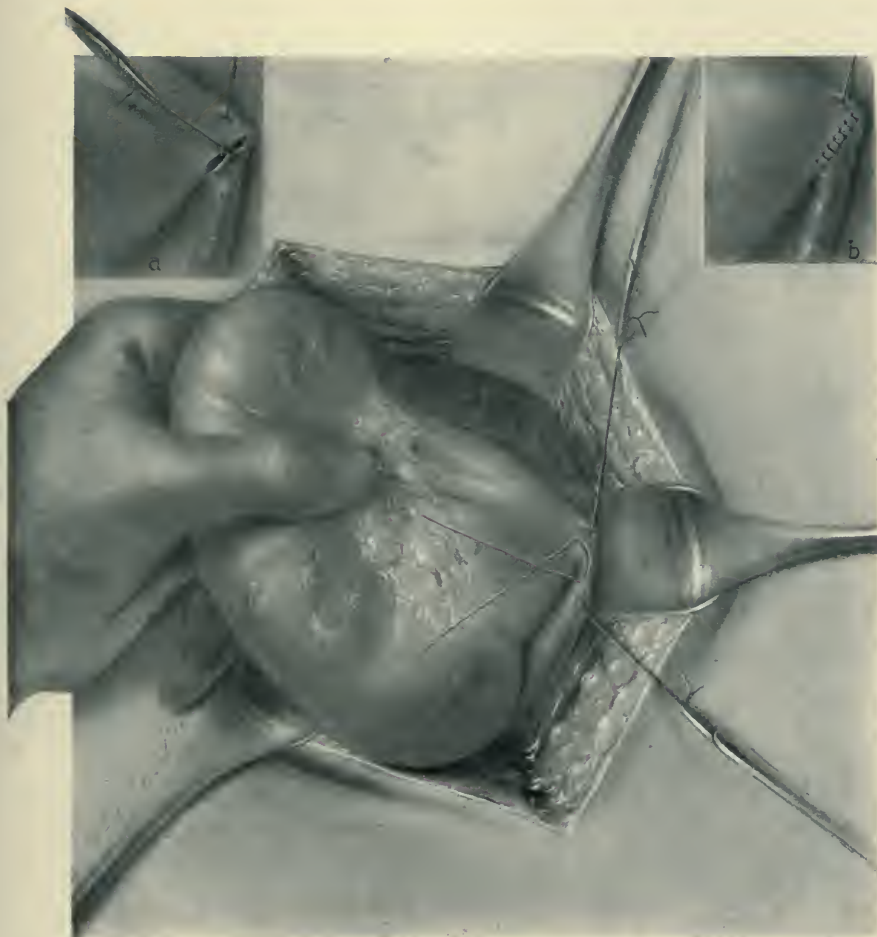


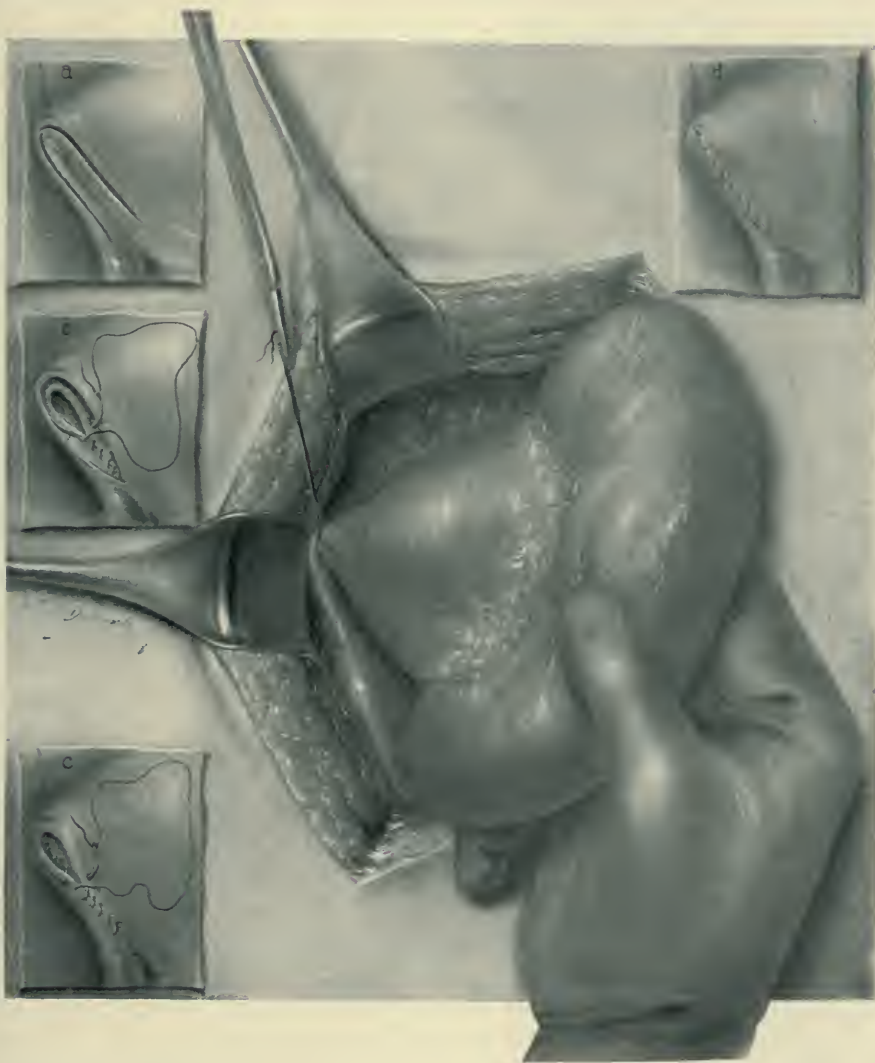
PLATE 8

SHOWING THE OPERATION FOR AMPUTATION OF THE UPPER URETER AND ANASTA-
MOSIS OF THE FREE END INTO THE RENAL PELVIS



PLATE 9

SHOWING THE VARIOUS STEPS IN THE PLASTIC OPERATION FOR THE CORRECTION OF EXTENSIVE NARROWINGS OF THE UPPER URETER



ON THE ABSORPTION OF DRUGS AND POISONS FROM THE BLADDER AND THE URETHRA

II. ABSORPTION OF VARIOUS ALKALOIDS, ANTISEPTICS, LOCAL ANESTHETICS AND SALTS

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In a previous communication (1), the author has shown that apomorphin and morphin furnish a very convenient method for the study of absorption from the bladder and the urethra, especially in the unanesthetized animal. It was further shown that these alkaloids are very poorly absorbed from the bladder but are very rapidly absorbed from the urethra, the posterior urethra being more efficacious than the anterior one in that respect. Following the observations on the absorption of morphin and apomorphin, the author undertook the study of the absorption of a large number of pharmacological agents from the same organs. The results of that study are to be reported in this communication. The substances studied include a number of alkaloids, local anesthetics, antiseptics and some salts. The method of study has already been described in the preceding paper. In the present communication the chief interest centers on the comparative absorptive powers of the bladder on the one hand and the whole urethra on the other. The difference in absorption between the posterior and anterior portions of the urethra were found in general to be the same as in the case of apomorphin and morphin, and for that reason further differentiation between the various part of the urethra in respect to their absorptive power is not gone into in the present paper. Inasmuch as most of the substances here studied are violent poisons, the great majority of the experiments were performed on anesthetized animals. A further

reason for the employment of anesthesia was the fact that in most of the cases blood pressure and respiratory tracings were made in order to study physiological signs of absorption of the drugs.

ON THE ABSORPTION OF SOME ALKALOIDS

The absorption of apomorphin and morphin has already been described in detail. Other alkaloids studied were atropin, cocaine, pilocarpin, aconitin, nicotin and epinephrin. Cocaine will be considered under the heading of anesthetics.

Atropin. As a criterion of the absorption of atropin, the author took advantage of its well known effect upon the nerve terminals or myoneural junctions of the parasympathetic nervous system and more particularly on the vagus endings in the heart. Even small doses of atropin when injected into an animal quickly paralyze the terminals of the vagi so that subsequent stimulation with the electric current is ineffectual in inhibiting the heart action. It was found that on introducing a solution of atropin sulphate 0.1 per cent into the bladder of a dog, care being taken to leave the catheter in position so as to prevent regurgitation or back-flow into the urethra, there was no demonstrable absorption of the alkaloid even as late as half an hour after the introduction of the drug into the bladder. Stimulation of the vagi with the electric current continued to inhibit the heart action exactly the same as in the normal animal. On the other hand, on irrigating the *urethra* with the same strength of solution of atropin sulphate, absorption took place in the course of a very few minutes, so that stimulation of the vagi required a greater amount of energy to produce the same inhibition and finally after a lapse of a longer interval could not be affected at all, thus indicating the complete paralysis of the vagi terminals in the heart. These results could be and were expressed in terms of absolute physical units by the use of a calibrated induction coil.

Pilocarpin. Ten cubic centimeters of a 1 per cent solution of pilocarpin hydrochloride introduced into the bladder of a dog were found to give no evidence of absorption even half an hour after the introduction of the drug, as evidenced by its specific

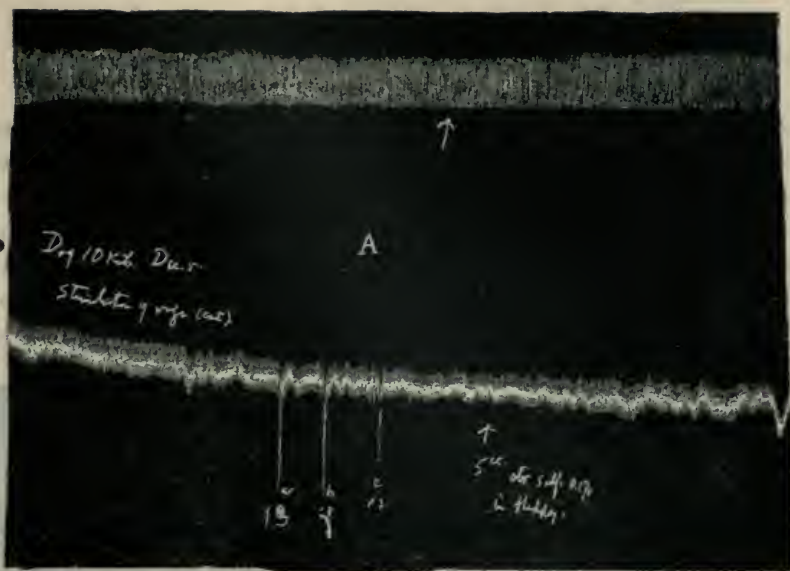


FIG. 1A. EFFECT OF 5 CC. OF ATROPINE SULPHATE (0.1 per cent) INTRODUCED INTO THE BLADDER

Note that stimulation with secondary in positions *a*, *b* or *c*, or 13 cm. from primary coil produces marked and immediate inhibition of the heart. This energy is equivalent to 1863 C. G. S. units. Central ends of vagi have been cut.

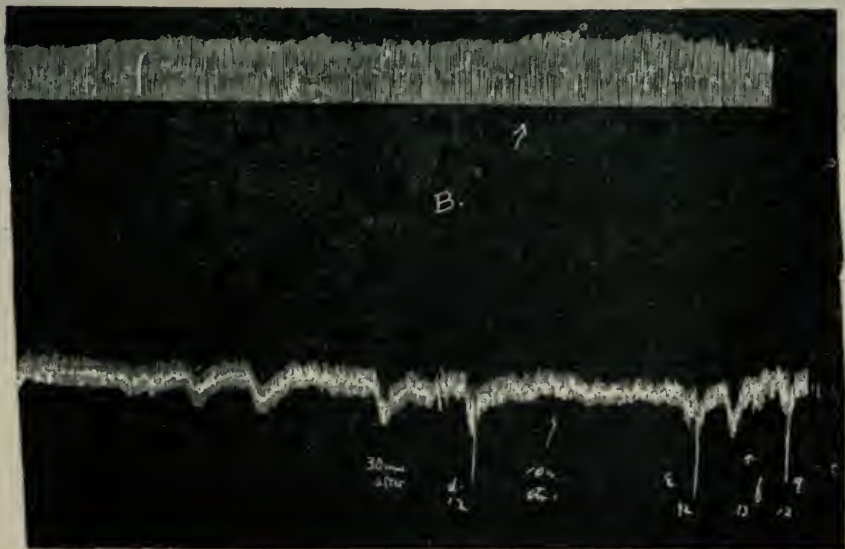


FIG. 1B. THIRTY MINUTES AFTER THE INTRODUCTION OF ATROPIN

No effect noted on terminals of vagi on stimulating at *d*. Ten cubic centimeters more of the alkaloid were then introduced with no effect on stimulating at *e*, *f* and *g*.

was followed by marked signs of absorption a minute later and death soon afterwards. This difference in absorption of nicotine from the bladder and the urethra is truly remarkable and can only be matched by the behavior of a solution of potassium cyanide in this respect, to be described later on.

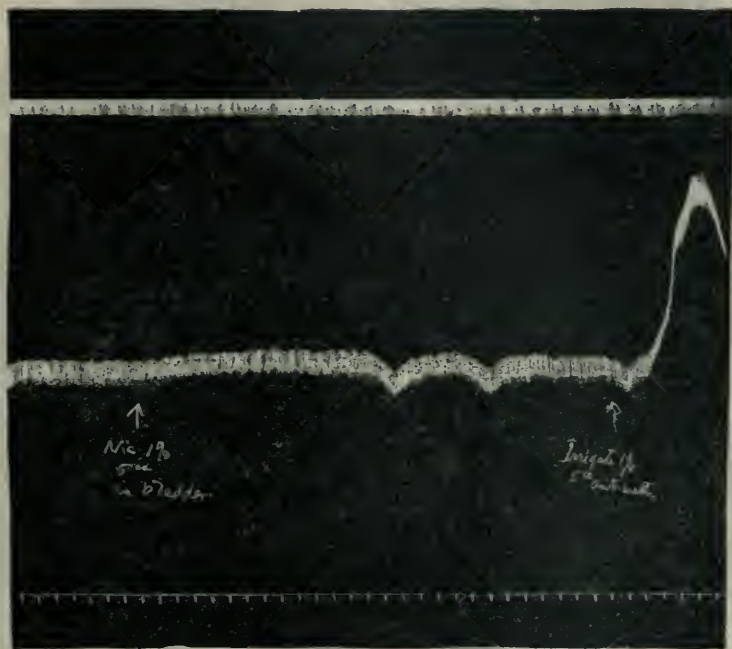


FIG. 3. FIVE CUBIC CENTIMETERS OF 1 PER CENT NICOTIN SOLUTION IN BLADDER SHOWS NO EFFECT

Irrigation of urethra with the same solution produces failure of respiration and heart.

Aconitin. This very powerful alkaloid also well illustrates the difference in absorption between the bladder and the urethra. The difference in the absorptive power of the two organs, however, cannot be sharply distinguished because of the paralyzing action of aconitin upon the sphincter muscles. On introducing 10 cc. of a 0.05 per cent of aconitin hydrochloride into the bladder of a large dog, there are at first no evidences of its absorption. Soon

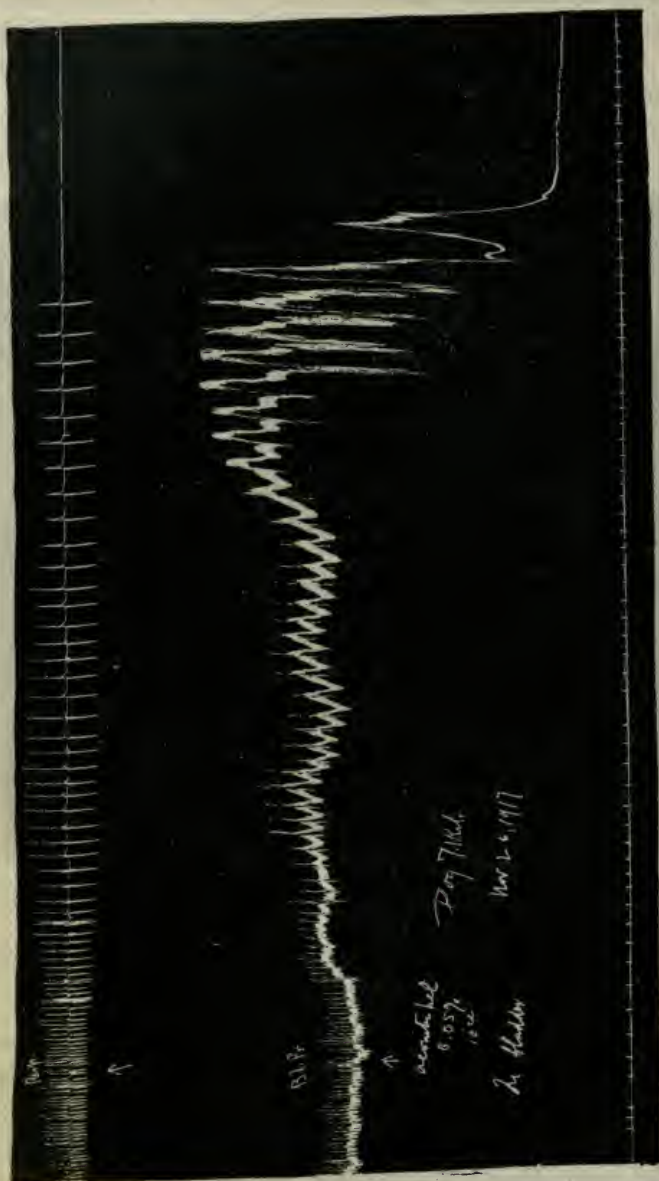


FIG. 4. ABSORPTION OF ACONITIN HYDROCHLORIDE FROM THE BLADDER OF DOG

however, it can be demonstrated that the internal sphincter of the bladder is relaxed and the solution of the alkaloid thus gets into the urethra and is followed by absorption of the drug, as shown by its effect on the circulation and respiration. That the alkaloid, however, is more rapidly absorbed from the urethra than from the bladder can be shown by irrigating the urethra with the same solution without pushing the catheter into the

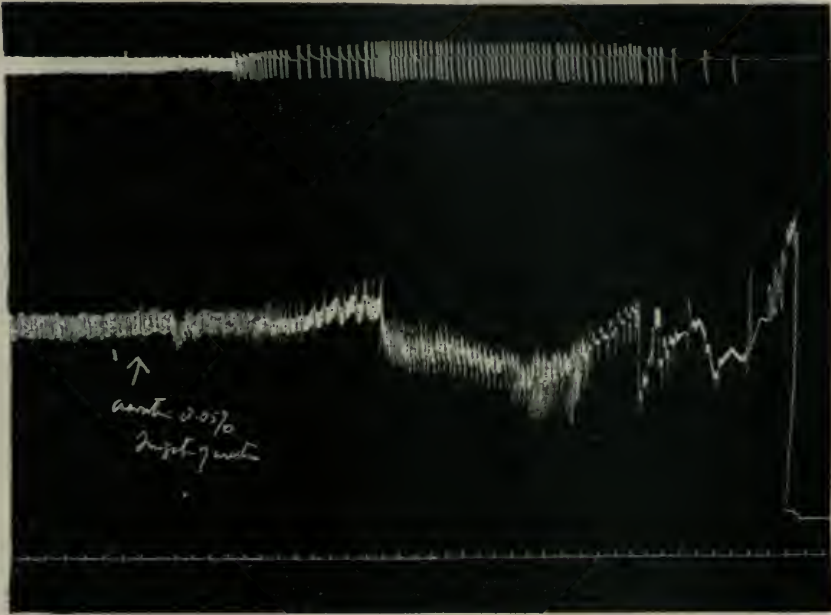


FIG. 5. ABSORPTION OF ACONITIN FROM THE URETHRA OF DOG

bladder. In such a case absorption from the urethra takes place more rapidly as is well illustrated by the figure 5.

Epinephrin. Epinephrin or adrenalin is used in the treatment of vesical and urethral hemorrhage; inasmuch as it is a powerful vasoconstrictor, little or no absorption of this alkaloid can be expected from any mucous surface. To make certain, however, of this point experiments were made with epinephrin in respect to its absorbability from the bladder and the urethra. It was found that on introducing 5 cc. or more of a 1:1000, solution of epi-

nephren into the bladder of a dog, no signs of absorption occurred. On irrigating the urethra, however, with even weaker solutions of adrenalin, enough of the drug *occasionally* (not always) was absorbed before the vessels were completely contracted, to produce a definite and characteristic rise in blood pressure, as shown by figure 6. It was furthermore found that the absorption of

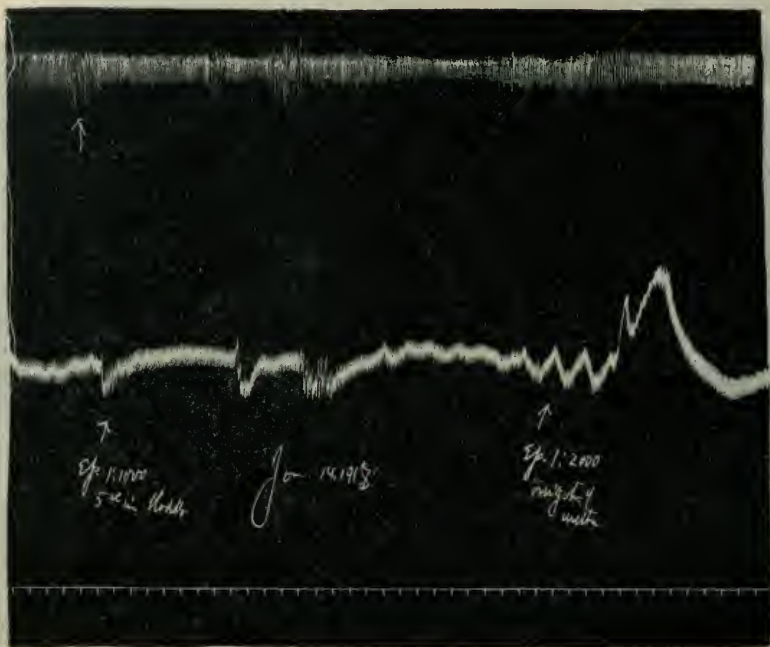


FIG. 6. EPINEPHRIN 1 TO 1000 ON INTRODUCTION OF 5 CC. INTO BLADDER PRODUCES NO EFFECT

Urethra of same dog irrigated with epinephrin 1 to 2000 shows some absorption.

epinephrin through the urethral walls could be facilitated by previous local treatment of the urethra with a solution of ergotoxin (fig. 7). As is well known, ergotoxin has the property of paralyzing the pressor or constrictor (but not the depressor or dilator) terminals of the true sympathetic nerves. This has been shown by the author to hold true also in excised or isolated blood vessels (2) On irrigating the urethra of a dog with a solution of

0.1 per cent of ergotoxin phosphate, it was found that a slight local paralysis of the vessels in the urethral walls was produced sufficient to enable a subsequent irrigation with an epinephrin solution to be absorbed more efficiently than in an animal not previously treated with ergotoxin. This same result could not be obtained by a similar treatment of the bladder. After prolonged irrigation of the urethra with a solution of ergotoxin, a sufficient amount of ergotoxin was absorbed through the urethra into the general circulation, in some experiments, to actually give a para-

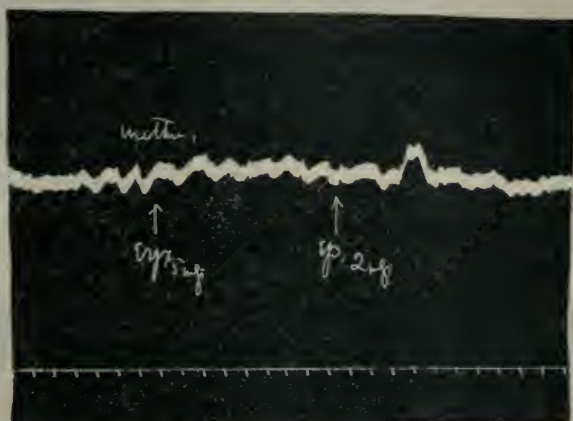


FIG. 7. IRRIGATION OF URETHRA OF DOG WITH ERGOTOXIN (5 MGM. IN 5 CC.) FOLLOWED BY EPINEPHRIN (2 MGM. IN 5 CC.)

doxical fall in blood pressure after a subsequent urethral irrigation with epinephrin. No such effect could be obtained in the case of the bladder.

ON THE ABSORPTION OF SOME ANTISEPTICS

Experiments were made with solutions of phenol (carbolic acid) and cresol. Irrigations of a dog's urethra with a 1 per cent solution of carbolic acid gave evidence of absorption as shown by a drop in blood pressure and shallowness in the respiration some fifteen minutes after the beginning of the experiment. Larger doses of phenol produced the same effect. The drop in blood pres-

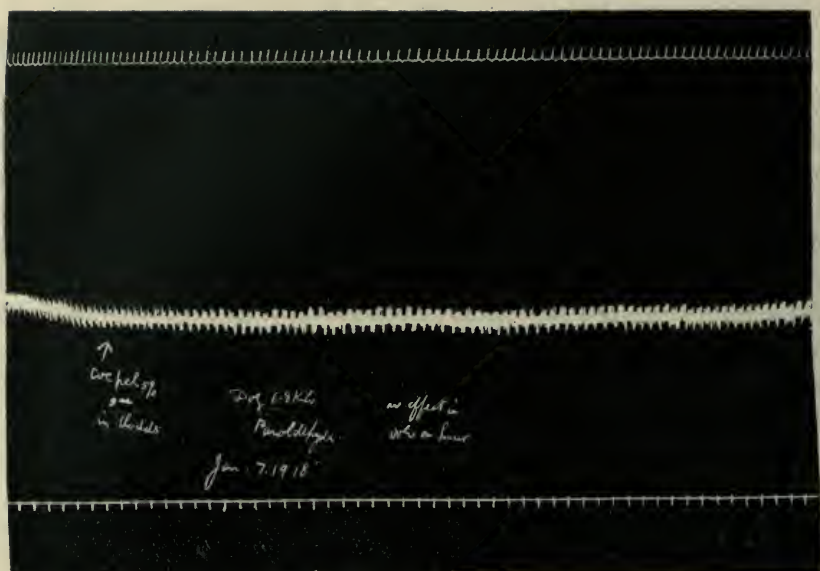


FIG. 8. FIVE CUBIC CENTIMETERS OF COCAIN HYDROCHLORIDE (5 PER CENT SOLUTION) IN BLADDER

Shows no change in blood pressure or respiration in over one hour.

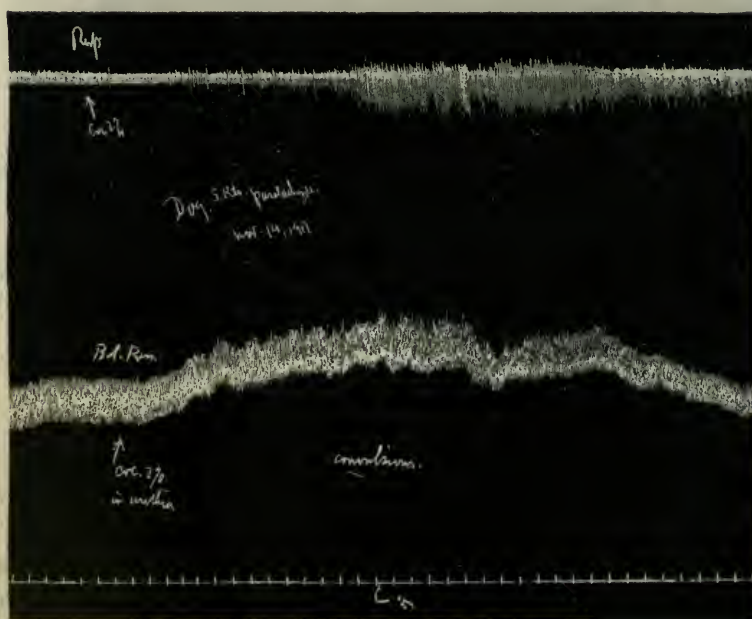


FIG. 9. URETHRA OF DOG IRRIGATED WITH 2 PER CENT COCAIN HYDROCHLORIDE

sure after phenol was not very marked yet gave evidence of a definite absorption of the drug from the urethra. The same concentration of phenol and even stronger solutions introduced into the bladder gave signs of no absorption after fifteen minutes or even

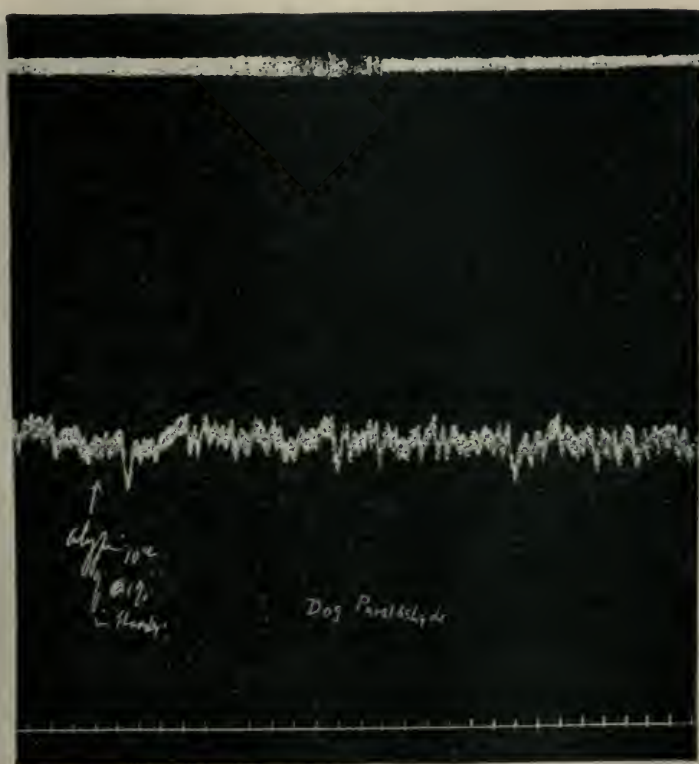


FIG. 10. EFFECT OF ALYPIN ON THE BLADDER ABSORPTION

Ten cubic centimeters of 0.1 per cent in bladder produces no effect.

longer. After longer periods of time, however, it was found that phenol apparently relaxed the sphincters, causing the penetration of the drug into the urethra and its subsequent absorption.

Experiments with cresol showed in general the same effect as phenol only in a lesser degree.

ON THE ABSORPTION OF SOME LOCAL ANESTHETICS

Only cocain and alypin were studied in this connection. It was found that the same difference in the absorptive power between the bladder and the urethra noted in case of other alkaloids held

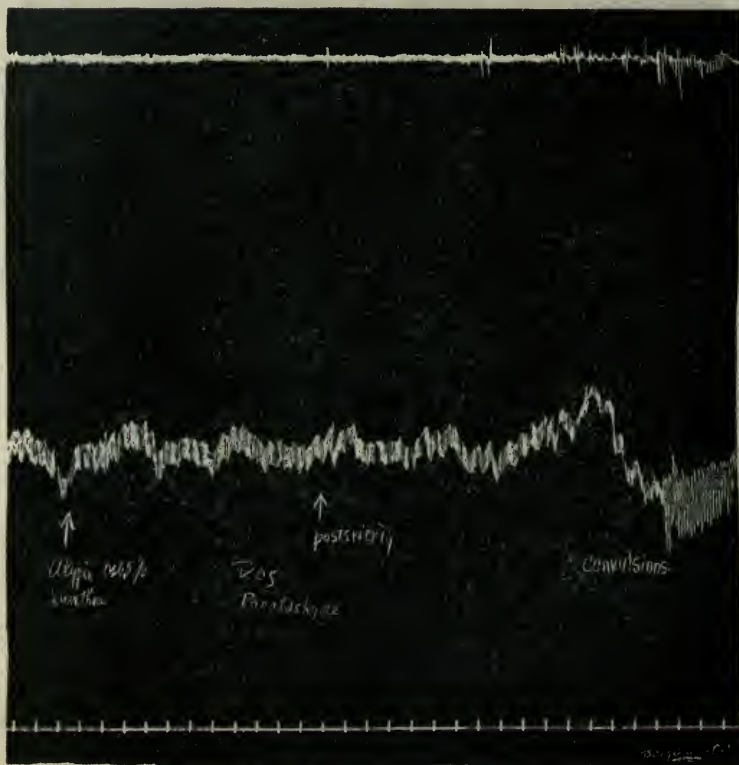


FIG. 11. ABSORPTION OF ALYPIN FROM URETHRA

Effect of irrigation with 0.05 per cent of the drug. Upper curve, respiration; lower curve, blood pressure.

good also in case of cocain and alypin. Thus in one experiment 5 cc. of a 5 per cent solution of cocain hydrochloride introduced into the bladder of a dog showed no signs of absorption as late as one hour after the beginning of the experiment (see fig. 8). On the other hand, irrigation of the urethra of another dog with a 2 per

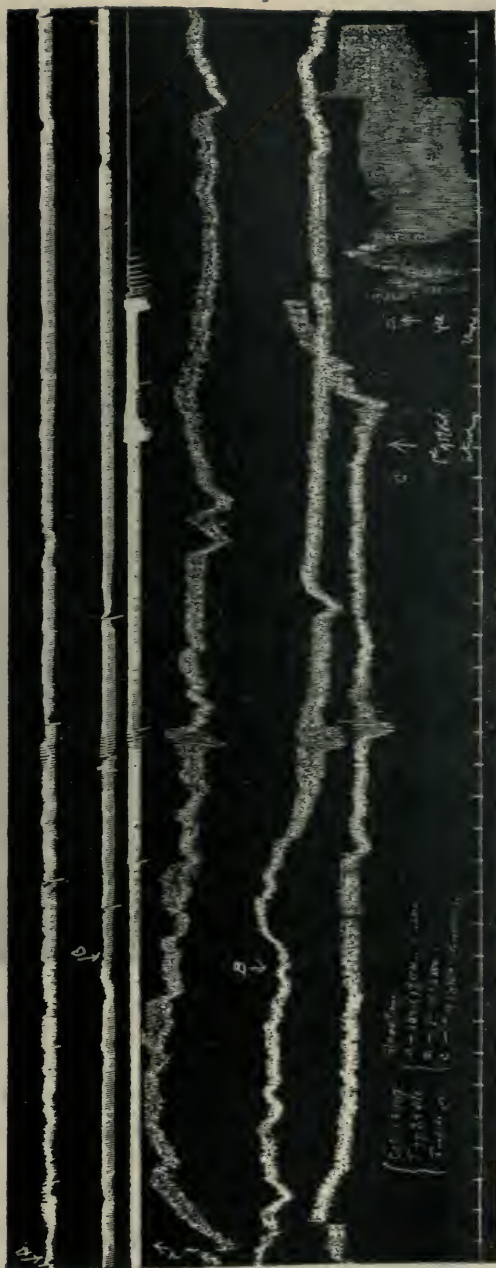


FIG. 12. POTASSIUM CYANIDE IN BLADDER OF DOG OF 7.9 KGM. HAS LITTLE EFFECT IN THE COURSE OF THREE HOURS
Upper three curves equals respiration; lower three curves equals blood pressure. At A 10 cc. of 1 per cent potassium cyanide is introduced into bladder. At B 5 cc. of 5 per cent potassium cyanide is introduced into bladder. At C animal killed by injection of 1 cc. of 1 per cent potassium cyanide in vein.

cent solution of cocain hydrochloride was soon followed by definite signs of absorption as shown by the effect on blood pressure and respiration and subsequent convulsions in the animal (see fig. 9).

Experiments with alypin were followed with exactly similar results. Unfortunately the supply of the drug was limited and only

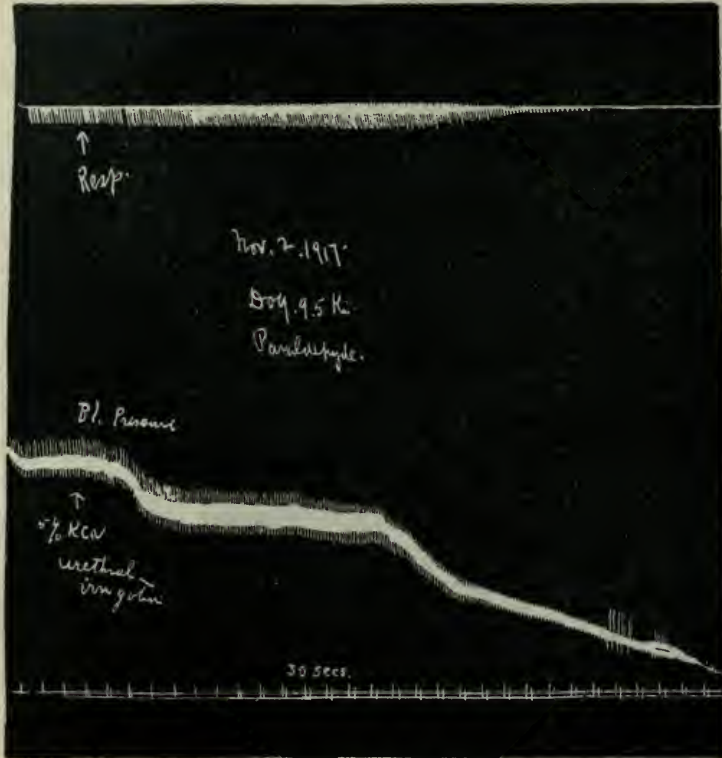


FIG. 13. ABSORPTION OF POTASSIUM CYANIDE ON IRRIGATION OF URETHRA OF Dog

weak solutions of it could be used, so that the curves are not as striking as in case of cocain (see figs. 10 and 11).

ON THE ABSORPTION OF POTASSIUM CYANIDE

In order to study the relative absorption of dissociable salts or electrolytes, solutions of potassium cyanide were employed by the

author in much the same manner as in the study of the absorption of that drug from the vagina (3). The difference between the absorptive powers of the bladder and the urethra can be demonstrated in a most remarkable manner by the use of this poison, as shown by figures 12 and 13. In one experiment (see fig. 12) 10 cc. of a 1 per cent solution of potassium cyanide was introduced into the bladder of a dog weighing 7.9 kilo and there was no sign of absorption evidenced for an hour or longer after introduction of the drug, as shown by the effect on the respiration and blood pressure, except for the primary reflexly irritating effect of the salt on the blood pressure. The first injection was followed by a second one (at *B*), this time of 5 cc. of a 5 per cent solution of the drug. This was also not followed by any marked absorption. At (*C*) 1 cc. of a 1 per cent solution of potassium cyanide was injected intravenously and was followed immediately by the characteristic paralysis of respiration and change in the blood pressure curve. In another experiment (see fig. 13) the urethra was irrigated with a 5 per cent solution of KCN, as shown in the figure and this was followed very quickly by absorption and rapid poisoning of the animal and death. From the study of the last two figures it will be strikingly evident that the absorptive powers of the bladder and the urethra are very different.

DISCUSSION

From the above described experiments it will be seen that a large number of drugs and poisons can be and are absorbed from the urethra. It is furthermore seen that the absorptive power of the bladder is very poor as compared with that of the urethra. These observations are not only of scientific interest but are also of practical importance. A review of clinical evidence agrees with the experimental findings described above. Poisoning through the urinary tracts has been reported and is not uncommon. On studying such cases it will be found that absorption of drugs or poisons in them occurred for the most part through the urethra. This holds good not only in case of the male, but also in the female. Absorption from the prostatic urethra in urological practice is not

unknown. In gynecology poisoning from the short female urethra has also been described. A well known gynecologist only recently communicated to the author the histories of two patients with idiosyncrasy toward cocain in whom he has observed definite signs of cocain poisoning after application of small amounts of it to the urethral orifice for the purposes of dilatation.

CONCLUSIONS

1. The absorption of a large number of drugs and poisons—alkaloids, antiseptics, salts and local anesthetics—from the bladder and the urethra in the male was studied.
2. It was found that the absorptive power of the bladder is very poor while absorption from the urethra takes place very rapidly and efficiently.
3. These facts are not only of a scientific interest but are of practical importance.

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- (2) MACHT: Journ. Pharm. and Exp. Therap., 1915, vi, 591.
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THE EFFECT OF THE ADMINISTRATION OF UREA ON THE RATIO BETWEEN THE RATE OF UREA EXCRETION AND THE CONCENTRATION OF UREA IN THE BLOOD IN EXPERIMENTAL GLOMERULO- NEPHRITIS

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Since the discovery by Schlayer and others (1) that the administration of various toxins causes a nephritis of either the tubular or vascular type, the study of nephritis along anatomical and physiological lines has shown progressive development. Pearce and others (2) definitely confirmed the above evidence in later work with dogs whereas the former investigators used rabbits. It is now well known that poisons such as chromate, uranium and sublimate affect the epithelial tissue producing extensive tubular injury. On the other hand, arsenic, catharidin and diphtheria toxin act to a greater extent on the vascular tissue and less on the tubules. The above workers noted that the excretion of nitrogen was diminished after the administration of tubular poisons. The retention of nitrogen in uranium nephritis without any increased excretion of fecal nitrogen was reported by Siegel (3). Austin and Eisenberg (4) noted the retention of nitrogen after the administration of large doses of uranium, cantharidin and chromate. Underhill and others (5) reported the same phenomenon in tartrate nephritis, which is of the same character as the uranium type.

In the early stages of nephritis the nitrogen excretion is not markedly altered; the output of urine, however, as Weber (6) and others have shown, is somewhat increased. Hellin (7) states that in artificial nephritis diuretics cause the kidney to excrete more urine than under normal conditions. In incipient nephritis, or even in the moderate grades of the disease, experimental and

clinical evidence shows that the kidney is more sensitive than usual. Pohl (8) described an increased elimination of water, sodium chloride and nitrogen in aristochin poisoning and Austin and Eisenberg (4) reported the same phenomenon in the nephritis produced by small doses of uranium. The experimental work of Mosenthal (9) likewise confirms this view. We (10) have also noted a greater permeability of the kidney in experimental uranium nephritis. There was a marked increase in water and an absolute and relative increase in nitrogen as compared with the blood nitrogen. The above facts show that it is impossible to determine accurately the function of the kidney by measuring the blood and urine constituents. Furthermore, one kidney is capable of performing the function of both kidneys in eliminating the end products of metabolism, as shown by Addis and Watanabe (11). Although the compensatory hyperactivity of the healthy tissue of the kidney may act in maintaining the balance of excretion, it leads one to believe that overworking the kidney by giving large quantities of urea, would cause a condition of fatigue in the surviving tissue. In this connection, Watanabe, Oliver and Addis (12), demonstrated a decrease in the ratio of the rate of excretion of urea to the amount in the blood after urea administration in uranium nephritis. Urea is excreted principally through the proximal convoluted tubular epithelium. Since the convoluted tubules are affected in uranium poisoning, in this type of nephritis there is a decrease of the ratio in a condition of kidney fatigue. However, this may not apply to the vascular type of lesion unless the flow of urine is greatly diminished.

The present work is to inquire whether or not the condition of kidney fatigue may be produced in experimental vascular nephritis by giving urea as the extra-renal factor.

METHODS

Rabbits were employed in this investigation. One or two days previous to the beginning of the experiment, the animals were fed cabbage and water freely; then after seventeen hours of complete starvation the experiment was begun. The work was re-

peated on each rabbit after a suitable interval. One week after the first period of the investigation, arsenious acid was administered subcutaneously in varying doses. Pearce and Brown (13) have demonstrated that this compound is more effective than other arsenicals in producing the vascular type of lesion in the kidney. Three days after the injection the second period of the investigation was begun.

For the determination of urea in the blood and urine, Addis and Watanabe's (14) modification of Marshall's method was employed.

Blood was drawn from the ear vein at 9 a.m. before giving urea and then hourly until 12 m., then again at 2 p.m. Urine was obtained by catheterization hourly from 9 a.m. to 12 m. and again at 2 p.m. At 9 a.m. 5 grams urea in 25 cc. of water were given by stomach tube. This procedure was followed in both periods of the investigation, that is, before and after the injection of arsenious acid. Duplicate results obtained from each rabbit were compared. After the estimations were completed, the animals were killed and the kidney prepared for histological examination.

The quantity of urea in the blood of normal rabbits varied from 24 mgm. to 61 mgm. in 100 cc. of blood and after the injection of arsenious acid there was a variation from 23 mgm. to 78 mgm. in 100 cc. of blood in the 16 rabbits used. After giving 5 grams urea to normal rabbits there is a sudden and enormous increase of urea as shown in table 1.

The increase in excretion of urea is roughly parallel to the increase of urea in the blood after giving urea. This is in harmony with human experiments, in which urea was given by mouth (14). The ratio of the rate of excretion of urea to the urea content in the blood was estimated for each hour's collection of urine. The average urea content of the blood was estimated from the samples drawn before and after the hourly sample of urine. This method is much more accurate than taking samples in the middle of the urine collection. The ratio of the rate of excretion of urea to the urea content in the blood was increased gradually in most cases, showing that the excretion is not strictly parallel to the concentration in the blood. If we compare the average ratio of

TABLE 1

The effect of the intake of 5 grams of urea on the ratio between the rate of urea excretion and the concentration of urea in the blood before and after the administration of arsenious acid in rabbits

RABBIT NUMBER	WEIGHT (GRAMS)	ARSENI- OUS ACID (MILLI- GRAMS)	TIME	AMOUNT OF UREA IN 100 CC. OF BLOOD		AMOUNT OF UREA IN URINE		VOLUME OF URINE		RATIO OF UREA UREA IN ONE HOUR'S URINE UREA IN 100 CC. OF BLOOD		AVERAGE RATIO OF UREA IN SECOND, THIRD AND FOURTH SPECIMEN	
				Before	After	Before	After	Before	After	Before	After	Before	After
				grams	grams	grams	grams	cc.	cc.	grams	grams		
2	1700	10	9 a.m.-10 a.m.	0.103	0.138	0.098	0.138	4.5	9.5	0.95	1.00		
			10 a.m.-11 a.m.	0.189	0.244	0.315	0.288	15.0	15.0	1.67	1.19		
			11 a.m.-12 n.	0.217	0.286	0.555	0.345	16.0	16.0	2.56	1.22		
			12 n. - 2 p.m.	0.211	0.308	1.032	0.750	30.5	28.5	2.44	1.22	2.22	1.21
14	1576	10	9 a.m.-10 a.m.	0.125	0.091	0.270	0.054	10.0	2.5	2.16	0.60		
			10 a.m.-11 a.m.	0.223	0.134	0.438	0.141	15.0	6.0	1.97	1.05		
			11 a.m.-12 n.	0.263	0.183	0.624	0.354	15.5	11.0	2.37	1.93		
			12 n. - 2 p.m.	0.245	0.240	1.254	1.128	24.5	30.0	2.56	2.35	2.30	1.78
1	1700	5	9 a.m.-10 a.m.	0.090	0.144	0.029	0.132	3.0	7.5	0.32	0.92		
			10 a.m.-11 a.m.	0.151	0.160	0.088	0.130	5.0	5.0	0.58	0.81		
			11 a.m.-12 n.	0.176	0.170	0.129	0.216	5.0	7.0	0.69	1.27		
			12 n. - 2 p.m.	0.200	0.180	0.462	0.738	17.0	22.0	1.16	2.05	0.81	1.38
4	1450	5	9 a.m.-10 a.m.	0.162	0.213	0.173	0.207	7.5	9.5	1.06	0.97		
			10 a.m.-11 a.m.	0.307	0.341	0.483	0.273	18.0	11.0	1.57	0.80		
			11 a.m.-12 n.	0.316	0.330	0.672	0.345	25.0	11.5	2.13	1.05		
			12 n. - 2 p.m.	0.276	0.325	1.074	1.002	32.0	30.0	1.95	1.54	1.88	1.13
5	1650	4	9 a.m.-10 a.m.	0.093	0.105	0.095	0.037	5.0	2.0	1.02	0.36		
			10 a.m.-11 a.m.	0.152	0.174	0.297	0.294	15.0	9.0	1.95	1.69		
			11 a.m.-12 n.	0.181	0.204	0.381	0.420	15.0	12.5	2.11	2.06		
			12 n. - 2 p.m.	0.192	0.235	0.702	1.176	21.5	33.0	1.82	2.50	1.96	1.91
7	1600	3.5	9 a.m.-10 a.m.	0.098	0.145	0.101	0.264	5.0	11.0	1.03	1.82		
			10 a.m.-11 a.m.	0.171	0.234	0.138	0.561	4.5	18.0	0.80	2.40		
			11 a.m.-12 n.	0.176	0.233	0.174	0.738	5.0	20.0	0.99	3.10		
			12 n. - 2 p.m.	0.190	0.268	0.708	1.200	18.0	27.0	1.87	2.20	1.22	2.57
8	1750	3	9 a.m.-10 a.m.	0.108	0.117	0.228	0.099	6.5	6.0	2.10	0.85		
			10 a.m.-11 a.m.	0.184	0.201	0.336	0.327	9.5	10.0	1.83	1.63		
			11 a.m.-12 n.	0.201	0.218	0.378	0.336	9.5	11.0	1.83	1.61		
			12 n. - 2 p.m.	0.208	0.227	0.948	0.870	45.5	30.0	2.28	1.92	1.98	1.72

TABLE 1—Continued

RABBIT NUMBER	WEIGHT (GRAMS)	ARSENIOUS ACID (MILLI- GRAMS)	TIME	AMOUNT OF UREA IN 100 CC. OF BLOOD		AMOUNT OF UREA IN URINE		VOLUME OF URINE		RATIO OF UREA IN ONE HOUR'S URINE UREA IN 100 CC. OF BLOOD		AVERAGE RATIO OF UREA IN SECOND, THIRD AND FOURTH SPECIMEN	
				Before	After	Before	After	Before	After	Before	After	Before	After
				grams	grams	grams	grams	cc.	cc.	grams	grams		
9 1850 2	{		9 a.m.-10 a.m.	0.112	0.088	0.201	0.174	8.0	6.0	1.80	1.98	2.21	2.62
			10 a.m.-11 a.m.	0.194	0.162	0.393	0.348	22.0	14.5	2.02	2.14		
			11 a.m.-12 n.	0.218	0.193	0.504	0.528	18.0	21.0	2.32	2.74		
			12 n. - 2 p.m.	0.228	0.197	1.044	1.152	22.0	41.0	2.29	2.92		
10 2000 2	{		9 a.m.-10 a.m.	0.114	0.110	0.102	0.159	6.0	8.0	0.90	1.45	1.71	2.57
			10 a.m.-11 a.m.	0.197	0.192	0.312	0.345	15.5	13.5	1.60	1.80		
			11 a.m.-12 n.	0.219	0.191	0.318	0.540	9.5	17.0	1.45	2.84		
			12 n. - 2 p.m.	0.223	0.196	0.948	1.200	21.0	28.0	2.08	3.06		
11 1700 1	{		9 a.m.-10 a.m.	0.080	0.118	0.140	0.162	5.0	7.0	1.76	1.38	2.15	2.05
			10 a.m.-11 a.m.	0.155	0.226	0.315	0.452	8.5	12.0	2.04	2.00		
			11 a.m.-12 n.	0.188	0.238	0.381	0.471	12.0	12.0	2.02	1.98		
			12 n. - 2 p.m.	0.191	0.242	0.924	1.046	22.0	25.5	2.38	2.16		
12 1900 1	{		9 a.m.-10 a.m.	0.115	0.139	0.093	0.162	3.5	5.0	0.81	1.16	1.84	1.95
			10 a.m.-11 a.m.	0.208	0.225	0.321	0.435	10.0	13.0	1.55	1.93		
			11 a.m.-12 n.	0.251	0.224	0.456	0.480	13.5	13.5	1.82	2.15		
			12 n. - 2 p.m.	0.253	0.212	1.092	0.798	26.5	20.0	2.16	1.82		
13 1655 0.5	{		9 a.m.-10 a.m.	0.124	0.089	0.174	0.102	9.0	8.0	1.41	1.15	1.68	0.65
			10 a.m.-11 a.m.	0.214	0.173	0.294	0.081	10.0	4.0	1.38	0.47		
			11 a.m.-12 n.	0.245	0.209	0.390	0.147	13.0	6.5	1.59	0.71		
			12 n. - 2 p.m.	0.240	0.225	1.002	0.348	28.0	10.5	2.08	0.77		

the second, third and third and fifth hour before and after the injection of arsenious acid in rabbits 2 and 14 which were given 10 mgm. of the drug, there was a decrease in both cases and when less than 5 mgm. was injected there was an increase, except in rabbits 4 and 13 which two rabbits showed a decrease, especially rabbit 13, which was given the smallest dose. Rabbit 13 had a diarrhoea after the injection of arsenious acid, and one may interpret the lack of greater increase of the urea in the blood

after arsenic injection over the increase in the blood after urea administration in normal animals, by the loss in the feces. Rabbit 4 which was administered 5 mgm. of arsenious acid showed a diminished ratio; there was a slight trace of albumin in the urine which was, however, more marked than in other cases where the drug was administered. One may judge that this dose of the drug might cause relatively severe anatomical damage to the terminal portion of the proximal convoluted tubules and thus diminish the excretion more than in other cases where the same dose was given, although histological examination failed to elicit any marked changes. It will be noted that the ratio generally increased after the injection of 5 mgm. or less in comparison with the first estimation. It is evident from this that the injection of small doses of arsenious acid stimulate the kidney to secrete more urea than normal.

A comparison of the volume of urine in the first five hours of periods 1 and 2, show little actual change except rabbit 13 which decreased markedly.

TABLE 2

The effect of the intake of 5 grams urea on the excretion of urea and water before and after the administration of arsenious acid in rabbits

RABBIT NUMBER	THE AMOUNT OF UREA EXCRETED FIVE HOURS AFTER THE ADMINISTRATION OF UREA, AND UREA AND ARSENIOS ACID RESPECTIVELY		THE AMOUNT OF URINE EXCRETED FIVE HOURS AFTER THE ADMINISTRATION OF UREA, AND UREA AND ARSENIOS ACID RESPECTIVELY	
	Only urea	Urea and arsenious acid	Only urea	Urea and arsenious acid
	<i>grams</i>	<i>grams</i>	<i>cc.</i>	<i>cc.</i>
2	2.00	1.52	66	69
14	2.60	1.68	65	50
1	0.71	1.21	30	42
4	2.40	1.83	83	62
5	1.47	1.93	57	57
7	1.12	2.76	33	66
8	1.88	1.62	46	57
9	2.14	2.20	70	83
10	1.68	2.24	51	67
11	1.76	2.13	48	57
12	1.96	1.88	54	52
13	1.86	0.69	60	29

Histological examination showed no pronounced degeneration or necrosis in the epithelial cells of the tubules. This is distinctly different from the uranium type of nephritis which acts especially on the tubular epithelium.

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The preparations of all the rabbits showed very much the same type of lesion and for this reason a detailed description is given for the typical appearance noted and brief mention made of the individual animals.

The most striking thing noted is the almost entire lack of severe epithelial damage. In none of the sections, even from those animals which had received large doses (10 mgm.) was any severe epithelial change seen. In practically all the specimens, however, there was seen varying degrees of granular degeneration in the epithelium. In none was it very pronounced, never approaching for example that seen in human kidneys and described as "cloudy swelling." This slight epithelial degeneration did not seem to be limited to any particular division of the proximal convoluted tubule. The ascending limbs of Henle's loop, the second convoluted tubule and the collecting tubules were normal.

The vascular lesions observed were slight, consisting of congestion. No definite hemorrhages were seen in any animals. The glomeruli showed pyknosis of their epithelial nuclei, and often the capsular space contained granular material.

Casts were found in practically all the tubules. They were of two kinds, granular, present in the proximal convoluted tubules and in the ascending limbs of Henle's loop and hyaline in the collecting tubules.

Rabbit 1. Very marked granular degeneration of epithelium. No vascular lesions. No casts. 5 mgm. of arsenious acid injected.

Rabbit 2. Marked congestion of glomeruli and vasa recta. Epithelium shows a slight granular degeneration. Few hyaline casts in collecting tubules. 10 mgm. of arsenious acid injected.

Rabbit 3. Moderate granular degeneration of cytoplasm of epithelium. No congestion. Few hyaline casts. Spontaneous nephritis present. 15

mgm. of arsenious acid injected. Died in convulsion one hour after injection.

Rabbit 4. Very slight epithelial degeneration. No vascular lesions. 5 mgm. of arsenious acid injected.

Rabbit 5. Same as rabbit 4. Slight spontaneous nephritis. 4 mgm. of arsenious acid injected.

Rabbit 6. Marked granular degeneration of epithelium. Lumina of proximal convoluted tubules contain much granular detritus. No vascular lesions. 4 mgm. of arsenious acid injected.

Rabbit 7. Moderate granular degeneration of epithelium. No vascular lesions. 3.5 mgm. of arsenious acid injected.

Rabbit 8. Moderate granular degeneration of epithelium. No casts, hemorrhage or congestion. 3 mgm. of arsenious acid injected.

Rabbit 9. Granular degeneration of epithelium marked. No vascular lesions or casts. 2 mgm. of arsenious acid was injected.

Rabbit 10. Same as rabbit 9. 2 mgm. of arsenious acid injected.

Rabbit 11. Marked granular degeneration of epithelium. Some granular material in capsular space of glomerulus. No casts. 1 mgm. of arsenious acid injected.

Rabbit 12. Marked granular degeneration. No vascular lesions or casts. 1 mgm. of arsenious acid injected.

Before the injection rabbit 5 had albuminuria and glycosuria and rabbit 6 had a severe glycosuria. There was a slight trace of albumin present in the urine of rabbit 7 before the experiment. After giving arsenious acid the urine was tested daily for albumin up to the fourth experimental day. There was a very slight trace of albumin in rabbits 2, 4 and 6, on and after the second day.

Throughout the above investigation, the excretion of urea from the kidney in incipient glomerulonephritis, produced by the injection of arsenious acid, does not change markedly from normal conditions in the same rabbit, although there is an increase in most cases where 5 mgm. or less were injected.

Rabbits showed a decreased excretion of urea when 10 mgm. of arsenious acid were injected.

CONCLUSIONS

In experimental incipient glomerulonephritis caused by the administration of small doses of arsenious acid, there is no

diminution in the ability of the kidney to excrete urea, even if a strain is caused by giving preformed urea.

The ratio of the excretion of urea in the urine to the concentration of urea in the blood is rather increased when small doses of arsenious acid are administered. We may thus conclude that after arsenic injection the kidney is in a state of hypersensitivity and does not show a state of fatigue.

The author acknowledges his indebtedness to Dr. J. Oliver of The Rockefeller Institute, for the examination of pathological specimens and for the writing of the report, and also to Prof. V. C. Myers, for allowing this work to be carried on in his laboratory.

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A NEW OPERATION FOR EPISPADIAS

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The great amount of literature which is found concerning the operative treatment of both hypospadias and epispadias is eloquent proof of the unsatisfactory results which have been usually obtained. This has been particularly true of epispadias.

In 1895, Cantwell presented a method for the operative treatment of epispadias by transplantation of the urethra to its normal position between and below the corpora, and forming "a penis normal in the relation of its component parts and normal in appearance." Cantwell's procedure was to build a urethral tube from the gutter-like groove on the dorsum of the penis, by bringing together the inner edges formed by two longitudinal incisions on either side of the groove. This newly-formed urethra was then dissected entirely free, and was dependent for its blood supply upon a very narrow pedicle at the base. He says, "a flap is formed of the whole urethra," and the latter is "held up out of the way while the cavernous bodies are separated either by light touches of the knife or by blunt dissection. The urethral flap is then laid in the gutter thus formed, and held in position by two sutures through mucous membrane and skin tied on under surface of the penis."

Without knowledge of the previous work which had been done, I performed, on November 3, 1913, a plastic operation which is somewhat similar though essentially different from Cantwell's operation described above. The technique which I employed is so graphically shown in the accompanying illustrations, that very little description is necessary. The conditions present before operation are shown in figure 1, the cross-section indicating the anatomical relations of the corpora cavernosa and the roofless urethra, and showing the groove along the dorsum of the penis,

extending from the urethral opening at the base of the penis to the glans. As seen in the accompanying diagrammatic cross-sections, it was evident at once that in order to restore the urethra to its normal position on the inferior surface of the penis beneath the corpora cavernosa, a procedure involving the separation of the corpora with transplantation of the new urethra would be necessary. In so doing it was also evident that the most important thing was to preserve the blood supply of the skin transplant, and I accordingly decided to leave this attached by a broad connection along its entire length to the left corpus cavernosum, and rotate this structure with the new urethra so as to displace the latter to its new position beneath the corpora. The transplantation was thus accomplished without serious interference with blood supply. This is graphically shown in figures 3, 4 and 5. As noted in figure 3, the corpora cavernosa have been well separated, so that they are held together only by the skin on the under surface of the penis. A very deep groove, to be occupied by the urethra, is thus produced. The left corpus has been sufficiently mobilized to allow it to be rotated; carrying with it the urethral graft. Figure 4 shows the formation of the new urethra from the skin of the dorsum of the penis, and also the attachment of the urethra to the left corpus. To close over the roof of the urethra a continuous chromic catgut suture is used. Figure 5 shows how the newly formed urethra is shifted to its new position beneath the corpora cavernosa simply by the bringing together of the two corpora above it, using interrupted sutures of chromic cat gut. The operation is then completed (fig. 6) by a dorsal line of sutures bringing together the two halves of the glans, and approximating the skin edges along the dorsum of the penis. A careful study of the semi-diagrammatic sectional views will give a clearer understanding of the various steps of the procedure and of the relation of parts than can be conveyed by any description. In order to divert the flow of urine, a perineal urethrotomy was done before the plastic operation was begun, and a retention catheter inserted. Perineal drainage was maintained for ten days.

The operation has now been done in two cases; the first I performed in November, 1913, upon a boy of seven, and the second

was done by E. G. Davis in October, 1917, upon a man of twenty-five. Neither operation differed essentially from the above-described technique, excepting that in the second case the procedure was handicapped by scar tissue, the result of two previous operative attempts. In each of these two cases the result was splendid, the patient obtaining a urethra situated, normally below the corpora, and with a meatus normally located on the glans. The patients voided normally with a good stream from the end of the penis, and had complete continence.

This procedure is remarkably simple and wonderfully satisfactory, and has the great merit of practically restoring the urethra to its normal location, and producing an almost normal external meatus. Although I was ignorant of Cantwell's work, the idea of transplantation of the new urethra is similar to his; but the plan of leaving the skin for the new urethra attached to one corpus cavernosum in order to secure adequate blood supply, and then rotating this structure, is quite original, and in fact the most important part of the procedure. Thus, a successful operation is practically assured by the removal of the one great defect which has been found to occur after Cantwell's operation, namely, death or atrophy of the skin transplant due to imperfect blood supply. Regardless of this, however, it is only fair to state that Cantwell cites two cases in which the results obtained were good, and in a discussion in the surgical section of the American Medical Association, following a paper by Bullitt, I find that Martin, Parham and Fenner reported satisfactory cases with Cantwell's method. Bullitt described a modification in which a longer urethra was obtained by utilizing the foreskin to form the distal portion, the remainder being furnished by Cantwell's technique.

My technique, which (although unconsciously similar) must be considered a modification of Cantwell's operation, furnishes, I think, a more surgical procedure, and one more likely to succeed owing to the better vascularity of the transplanted new urethra of dorsal skin.

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PLATE 1

FIG. 1. CONDITION BEFORE OPERATION

The only evidence of a pendulous urethra is a groove on the dorsum of the penis, lined by urethral mucosa which is sharply demarcated from the skin covering the remainder of the penis. Cross section shows relation of groove to corpora.



PLATE 2

FIG. 2. SKIN INCISION

The penis is held in position by two sutures placed in glans (*G*). As indicated by the black line in the diagrammatic cross section, the incision on the left side goes only through the skin and down to the corpus, while, on the right, the dissection is carried down between the corpora until the skin of the under surface of the penis is reached.

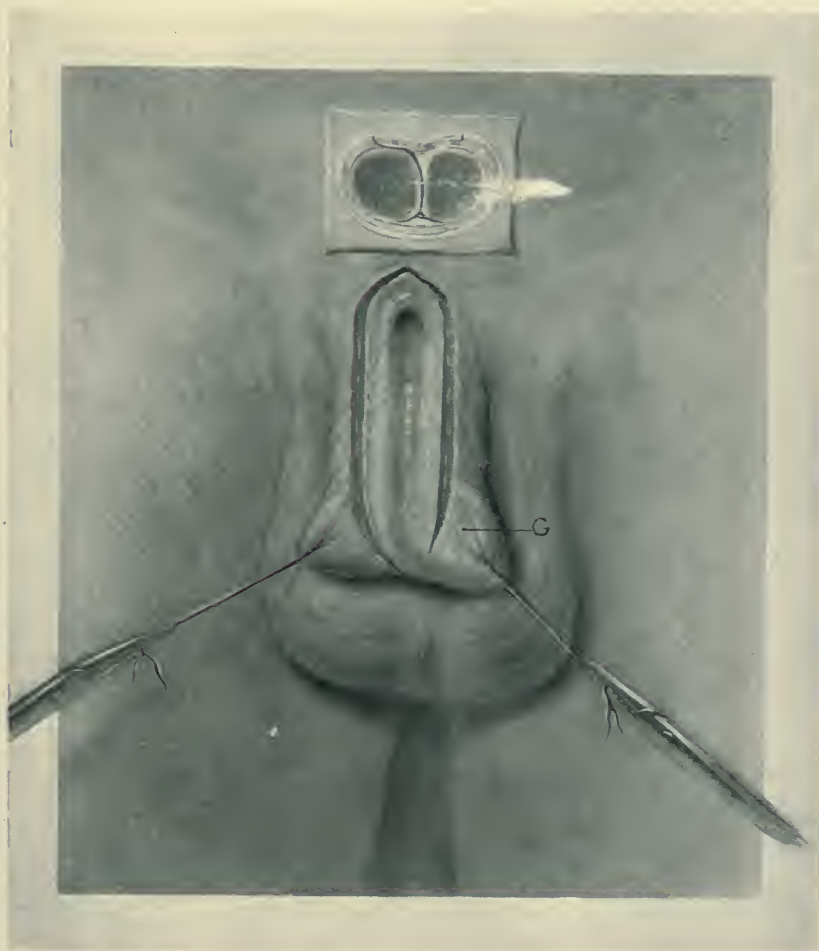


PLATE 3

FIG. 3. THE SEPARATION OF THE TWO CORPORA HAS BEEN COMPLETED

The skin edge is being retracted to the right and the edge of the new urethra to the left, exposing the right corpus (*C*) and exposing also the space between the two corpora, the floor of which is formed by the inner surface of the skin of the under surface of the penis. The relations are clearly indicated in the cross section.



PLATE 4

FIG. 4. THE NEW URETHRA IS BEING FORMED BY A CONTINUOUS SUTURE, BRINGING TOGETHER, OVER A CATHETER (*Ca*), THE EDGES PRODUCED BY THE ORIGINAL INCISION, AND CONVERTING THE ORIGINAL GROOVE INTO A TUBE

The attachment of the urethral tube to the left corpus may be distinctly seen both in surface view and cross section.

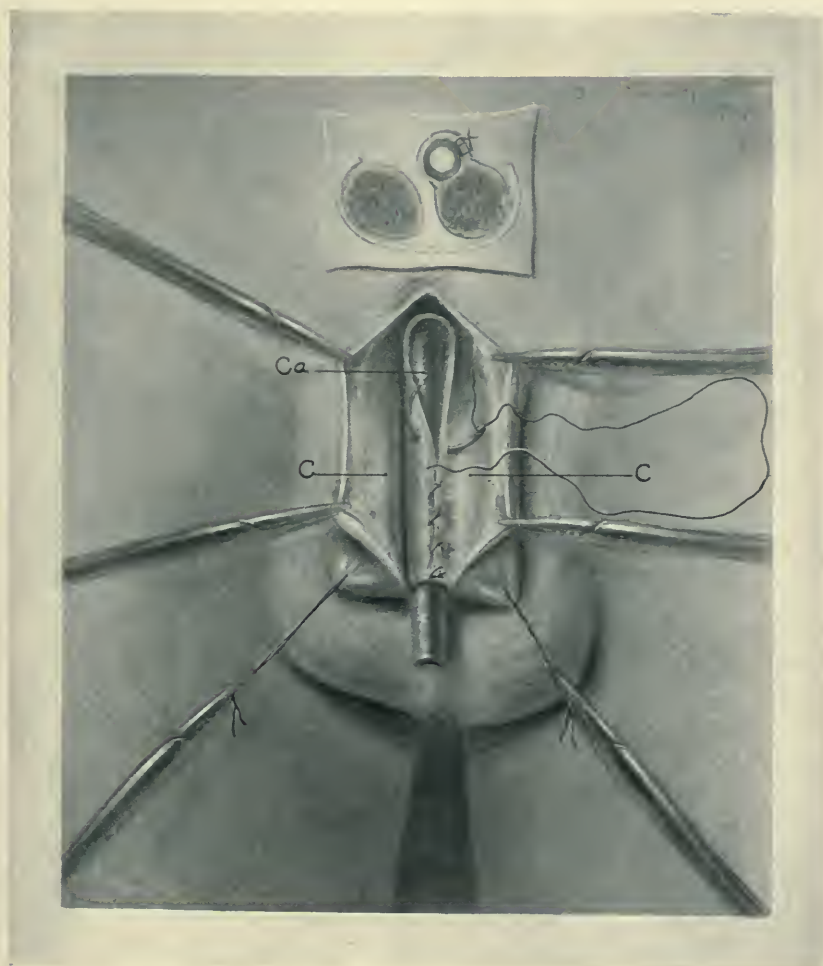


PLATE 5

FIG. 5. THE RIGHT CORPUS (C) HAS BEEN ROTATED, CARRYING THE URETHRA DOWN TO ITS NEW POSITION BELOW AND BETWEEN THE TWO CORPORA

The latter are being sutured with interrupted sutures of chromic cat gut. The unfinished suture-line above permits a view of the underlying newly formed urethra.

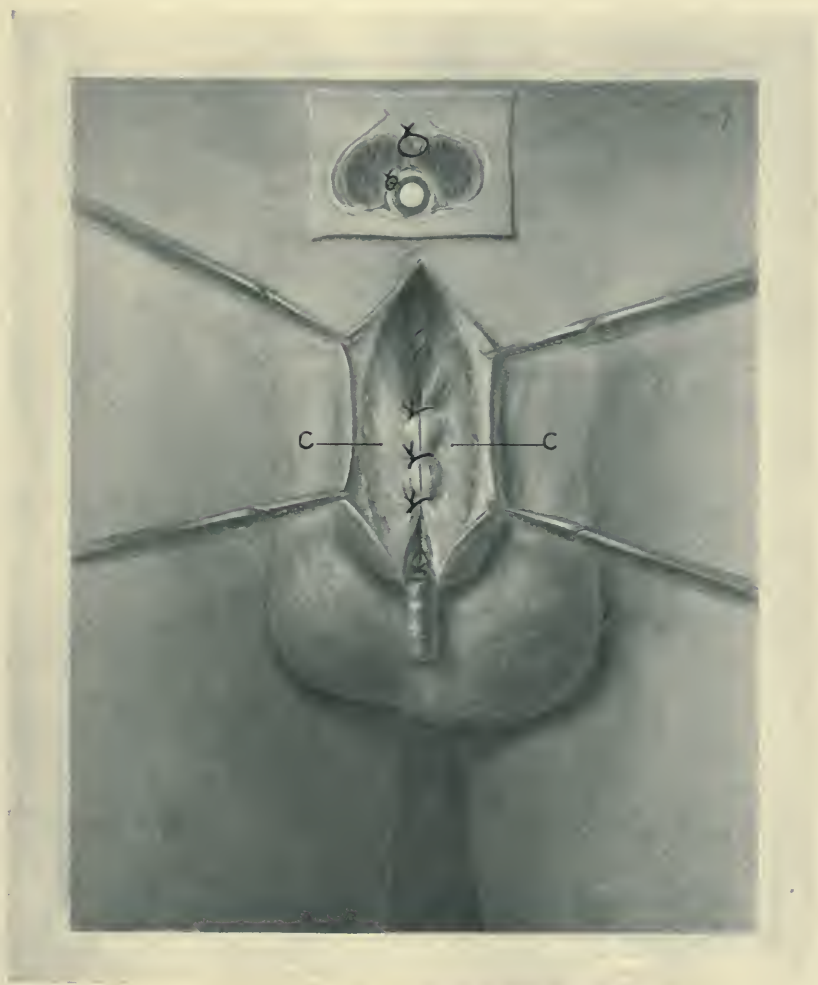
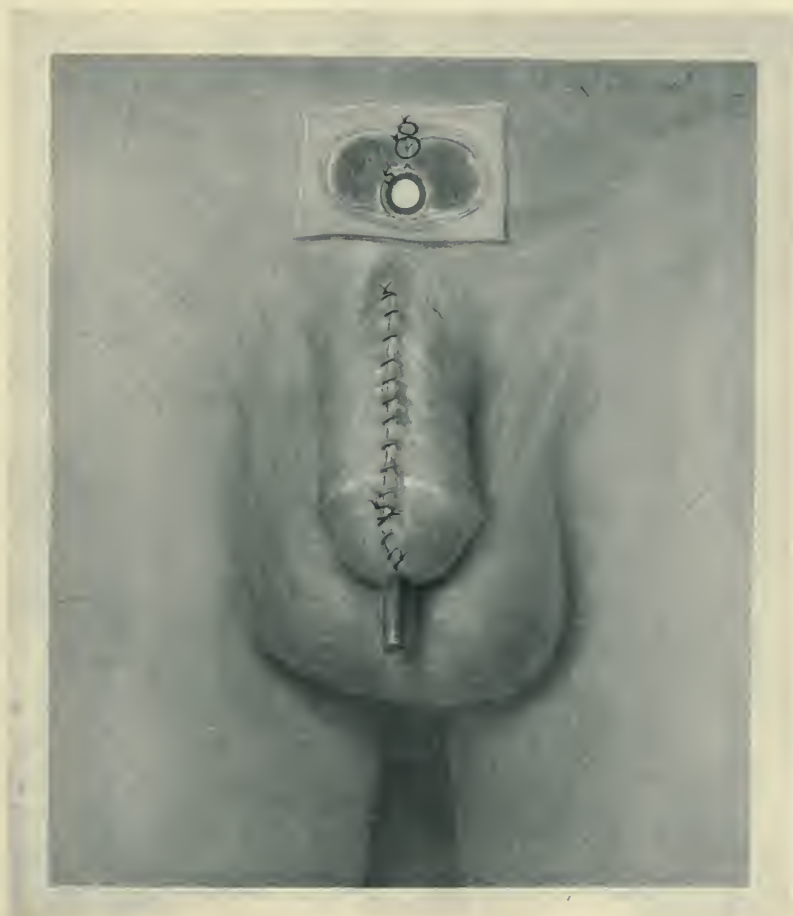


PLATE 6

FIG. 6. THE OPERATION COMPLETED

The two outer edges of the original incision were easily brought together in the midline making a penis and glans almost normal in appearance.



A FLEXIBLE METALLIC URETERAL SOUND WITH FILIFORM GUIDE

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The interest shown of late by urologists in studying more assiduously the pathological conditions of the ureter has brought to light many points of interest concerning this most important structure. Aside from the question of ureteral calculus, it has been the common conception that the ureter remained singularly free from any intrinsic pathological processes, at least their occurrence was considered relatively infrequent. Recent investigations however, particularly as regards the prevalence of ureteritis and ureteral stricture, have shown beyond a doubt, that the ureter is the seat of trouble much more frequently than was once supposed and that we will have to revise our texts on this subject.

Those who have done any amount of ureteral catheterization and sounding have encountered cases in which it was found impossible to introduce ordinary sized ureteral catheters into the ureter as far up as the renal pelvis. Catheters might possibly enter the ureter for a few centimeters but then some definite obstruction would be met with which no amount of manipulation would overcome. That some of these cases were correctly diagnosed as ureteral kinks, no one will question; but that the majority of them were of this character, is certainly open to discussion. Before the day of the x-ray, the opaque catheter and thorium solution, these mistakes were permissible, but today with these valuable aids at our command, errors in diagnosis of ureteral conditions should be the exception, not the rule.

The ingenious instruments that have been introduced by urologists during the past few years, for the detection and correction of ureteral obstructions, are numerous. The graduated catheter of Garceau, the high frequency olives of Buerger, the electric

filiform of Geraghty and the two- and four-bladed dilators of Bransford Lewis have been among those most popular. All of these instruments are employed through the operating cystoscope which accommodates instruments up to the size of No. 11 of the Charrière scale.

Where one is dealing with an obstruction of a type which permits introduction of such instruments as these, success will usually crown the efforts at dilatation. Where the operator meets with failure however, as is apt to occur when dealing with ureteral strictures of small caliber, a fine-pointed filiform will be required to achieve the desired result. Yet where the filiform alone is passed, little dilatation will result. For this reason the writer

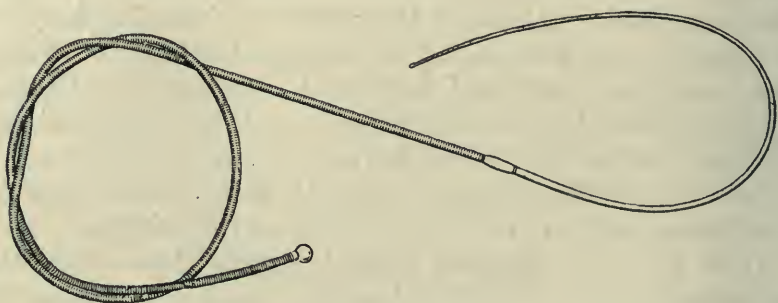


FIG. 1. VIEW OF FLEXIBLE METALLIC URETERAL SOUND WITH FILIFORM GUIDE

interested himself in this subject particularly, with the aim of assisting the cystoscopist to more readily overcome difficult ureteral obstructions. The efforts have been partially successful.

Adopting the principle which Le Fort introduced in his flexible silk filiforms with metal sound followers, the two being joined by a screw-thread connection, the writer had constructed a flexible metallic ureteral sound, the length of a ureteral catheter, with a semi-olivary tip of the size 11 Charrière, the extremity of the tip being a screw-threaded projection to join on to any ordinary Le Fort filiform guide. The shaft of this ureteral sound being flexible, has all the resiliency of any catheter or other instrument, constructed for use through an operating cystoscope, with the added advantage that it possesses infinitely more rigidity than a

silk instrument. Two lengths of filiforms are desirable. A long one to be used when dilatation is to be produced near the bladder and a shorter one to be employed when the dilating olive must be passed far up the ureter near the kidney. It should be stated in passing that no trauma to the kidney pelvis has ever been evidenced by the writer while using these filiforms in this manner. As the obstruction point is usually at the uretero-vesical juncture or just above this portion of the ureter, it will not necessitate introducing the filiform so far up as to curl in the renal pelvis.

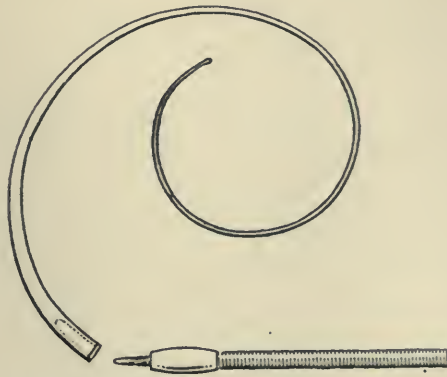


FIG. 2. SAGITTAL VIEW OF TERMINAL END OF FLEXIBLE METALLIC URETERAL SOUND SHOWING OLIVARY TIP AND METHOD OF CONNECTING SAME TO THE FILIFORM GUIDE

Where the obstruction is near the kidney, the short filiform is used.

The technique employed in passing this sound is simple. With the operating cystoscope in a water-distended bladder, having located the ureteral orifice, the filiform guide, firmly screwed on to the flexible sound, is fed into the catheter channel of the cystoscope. After the filiform enters the bladder, catheterization is attempted in the usual way. Naturally the finer the tip of the filiform, the more readily one is apt to get through the ureteral stricture or other obstruction. The writer has found the LeFort filiforms much firmer in consistency than the usual ureteral filiforms now in use. By manipulating the filiform with a cork-screw

motion, one will frequently succeed in getting through even the most severe type of stricture when passage up the ureter could not be accomplished in any other way. Once the filiform passes the narrow point, the instrument can then be pushed up the ureter until the olivary tip engages the stricture, dilating it to 11 Charrière.

ACRIFLAVINE IN THE TREATMENT OF GONORRHOEA—AN EXPERIMENTAL AND CLINICAL STUDY

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PART I

BY E. G. DAVIS

During the course of an investigation of the properties of a large number of compounds, with the purpose of finding a drug suitable for use as an internal urinary antiseptic (Davis (1), Davis and White (2), Davis, White and Rosen (3)), it was noted that some of these compounds possessed the property of rapid diffusibility through the tissues. In all, more than two hundred compounds were investigated, many of which were triphenylmethanes, but most of which were synthetic compounds related to sulphonphthaleins, nearly all of them being highly colored. The rate of renal elimination of each one of these compounds was determined by injection into the ear vein of rabbits, and it was during this procedure that the diffusibility became apparent. Most of the compounds remained confined to the vein into which injected, and passed immediately into the general circulation. An occasional one, however, would spread rapidly from the larger vein into the minute capillaries, and within a very few seconds dye the entire ear a homogeneous color. It was very surprising to observe how the edge of this wave of color would rapidly advance (like a blush) until the ear was completely dyed. Of the entire number of compounds investigated, in about ten this phenomenon was observed, these ten exhibiting varying degrees of diffusibility. As suggested by Dr. J. T. Geraghty, the ideal drug to be used as an injection in

the treatment of urethritis should possess just this property; that is, rapid diffusibility and penetration of the tissues.

Concerning the antiseptic properties of these diffusible drugs (as has been pointed out in the above mentioned publication), many of them are germicidal in high dilution *in water*, but almost all of them lose this property, wholly or partially, when diluted *in urine*. Of the entire number, about a dozen retained their antiseptic action to some extent, and, of these, four were both antiseptic and diffusible, and hence were experimentally indicated as being worthy of trial in the treatment of gonorrhea. These compounds were malachite green, brilliant green, proflavine and acriflavine, of which the last, acriflavine, was found to be antiseptic in the highest dilution of them all. This drug was also among the most diffusible.

BACTERIOLOGICAL TECHNIQUE

In determining the antiseptic and germicidal strength of these drugs in urine, both acid and alkaline urines were used. The necessity for this has been pointed out in previous publications; and, furthermore, Shohl and Janney (4) have shown how important is a variation in the reaction of urine (used as a culture medium) in influencing the rate of growth of the colon bacillus. It was therefore desirable to devise a method of adjusting the reaction of voided urine so that, from day to day, specimens of both acid and alkaline urine would be available, each of a constant hydrogen ion concentration. The object was not only to know that a specimen of urine used for antiseptic tests on a certain day was acid or alkaline, but also to know the exact degree of acidity or alkalinity, as measured by the hydrogen ion scale. Henderson and Palmer (5) have shown that the hydrogen ion concentration of urine is normally subject to a considerable range of variation (p_H 4.8 to p_H 7.4), and that the average of this range is p_H 6.0 on the hydrogen ion scale, corresponding to 0.000001 N acid. Each sample of urine to be used for cultural purposes was voided by a normal individual into a sterile (second) flask, and adjusted to the desired reaction

by titration with tenth normal acid or alkali, the end-points being determined by the colorimetric method; that is, by comparison with a standard hydrogen ion scale made up with solutions of buffer salts, colored by the sulphonphthalein series of indicators. (See publications by Clark and Lubs (6), and Shohl and Janney.) The end-points arbitrarily chosen were p_H 6.0 on the acid side (indicator, dibromcresolsulphonphthalein) and

TABLE 1
The antiseptic strength of acriflavine in urine

DILUTION OF DRUG IN URINE	COLON BACILLUS		STAPHYLOCOCCUS AUREUS	
	Acid urine (p_H , 6.0)	Alkaline urine (p_H , 8.0)	Acid urine (p_H , 6.0)	Alkaline urine (p_H , 8.0)
1: 200	0	0	0	0
1: 500	0	0	0	0
1: 1,000	0	0	0	0
1: 5,000	0	0	0	0
1: 7,500	∞	0	0	0
1: 10,000	∞	0	0	0
1: 20,000	∞	0	0	0
1: 30,000	∞	0	0	0
1: 30,000	∞	0	0	0
1: 50,000	∞	0	0	0
1: 75,000	∞	0	0	0
1: 100,000	∞	0	?	0
1: 200,000	∞	?	∞	?
Control of drug-free urine.....	∞	∞	∞	∞
Phenol, 1: 1,000, in urine.....	∞	∞	∞	∞

The dilutions were inoculated and incubated at 37°C. for twenty-four hours, after which 0.1 cc. was transferred from each tube to melted agar, and plated. Columns indicate number of colonies in plates.

0 = no colonies; ∞ = infinite number of colonies; ? = inconstancy of results, as shown by experiment repeated several times.

p_H 8.0 on the alkaline side (indicator, phenolsulphonphthalein). By this method we were able to say with certainty that the hydrogen ion concentration of specimens of acid (p_H 6.0) urine and of alkaline (p_H 8.0) urine, used for antiseptic tests, did not vary from day to day.

Antiseptic strength in urine. Dilutions were made in sterile test tubes with sterile pipettes, and each dilution inoculated

with one standard loop of a twenty-four hour broth culture. Parallel experiments were run, using the colon bacillus with one set of dilutions and the staphylococcus aureus with the other. The inoculated dilutions were then incubated for twenty-four hours, after which 0.1 cc. of urine was transferred from each tube (with a sterile capillary pipette) to melted agar, and plated. Plates were inspected after twenty-four hours and again after forty-eight hours. The results obtained for acriflavine and proflavine are shown in tables 1 and 2. Those plates showing

TABLE 2
The antiseptic strength of proflavine in urine

DILUTION OF DRUG IN URINE	COLON BACILLUS		STAPHYLOCOCCUS AUREUS	
	Acid urine (p _H , 6.0)	Alkaline urine (p _H , 8.0)	Acid urine (p _H , 6.0)	Alkaline urine (p _H , 8.0)
1: 200	0	0	0	0
1: 500	0	0	0	0
1: 1,000	?	0	0	0
1: 10,000	∞	0	0	0
1: 20,000	∞	0	0	0
1: 30,000	∞	0	0	0
1: 50,000	∞	?	0	1000
Control of drug-free urine.....	∞	∞	∞	∞
Phenol, 1: 1,000, in urine.....	∞	∞	∞	∞

The dilutions were inoculated and incubated at 37°C. for twenty-four hours, after which 0.1 cc. was transferred from each tube to melted agar, and plated. Columns indicate number of colonies in plates.

0 = no colonies; ∞ = infinite number of colonies; ? = inconstancy of results, as shown by experiment repeated several times.

no colonies, or very few, proved that there had been inhibition of development during the incubation period; while those showing countless numbers of colonies (designated by the infinity sign, ∞) proved that growth had taken place.

The striking feature brought out by these tables is the comparative weakness of acriflavine and proflavine in inhibiting the growth of the colon bacillus in *acid* urine, as contrasted with the extremely high dilution in which these drugs are effective against the same organism in *alkaline* urine. The staphylococcus aureus, however, is inhibited by both drugs in high dilution in

both acid and alkaline urine. These tables are not based on only one experiment. The entire series of dilutions of both drugs, using urine of the same degree of acidity and alkalinity, was repeated several times on different occasions. In some of the higher dilutions (as indicated in the tables by a question mark), there was an inconstancy of results demonstrated by this repetition. For instance, the effect of acriflavine, in a dilution of 1:200,000, upon the staphylococcus aureus in alkaline urine (p_H 8.0) was determined four times on four different occasions. Three times the organism was killed, and once there was a profuse growth. It cannot be said what variable factor played a part here, unless it might have been a variation in the specific gravity of the urine. It is certain, however, that the organism, the temperature, the dilution, and the hydrogen ion concentration were constant factors. Furthermore, the daily control of drug-free urine, both acid and alkaline, invariably showed a profuse growth. Less extreme dilutions exhibited no such inconstancy. There can be no question that in alkaline urine acriflavine will inhibit the development of both the colon bacillus and staphylococcus aureus in a dilution of 1:100,000. In acid urine, acriflavine is almost as effective against the staphylococcus, but will not inhibit the colon bacillus in a dilution much greater than 1:5000. Even this, however, is more than five times as effective as carbolic acid.

Germicidal strength in urine. The method here employed was the same in every respect as that for the antiseptic test, except that the inoculated dilutions were incubated for only one hour instead of for twenty-four hours. One hour was simply an arbitrarily chosen period of time. Acriflavine only was investigated by this method. As shown in table 3, a 1:10,000 dilution failed to kill either the colon bacillus or the staphylococcus aureus, either in acid or alkaline urine; while in acid urine even a 1:500 dilution failed to kill the colon bacillus. The weakness of acriflavine against the colon bacillus in acid urine is therefore a constant feature in both antiseptic and germicidal tests. From table 3 it may be concluded that acriflavine is not *rapidly* germicidal; its value lies in its antiseptic power.

Inhibition of gonococcus. In determining the concentration of acriflavine necessary to inhibit the gonococcus, testicular infusion agar, prepared according to the method described by Hall (7) was used. For this media, for the gonococcus cultures, and for assistance in examining sub-cultures and Gram stains, we are indebted to Dr. E. A. Greenspon, of the Department of Pathology, Johns Hopkins Hospital. Various dilutions of acriflavine, proflavine, phenol, argyrol, and protargol were made in tubes of testicular infusion agar, and the latter slanted and cooled. The method was to make up the testicular infusion agar in tubes, each containing 4 cc., and to add to each (while melted) 1 cc. of sterile water containing in solution the neces-

TABLE 3
The germicidal strength of acriflavine in urine

	COLON BACILLUS		STAPHYLOCOCCUS AUREUS	
	Acid urine (pH, 6.0)	Alkaline urine (pH, 8.0)	Acid urine (pH, 6.0)	Alkaline urine (pH, 8.0)
Dilution which kills in 1 hour.....	1: 200	1: 1,000	1: 1,000	1: 1,000
Dilution which fails in 1 hour.....	1: 500	1: 10,000	1: 10,000	1: 10,000

sary amount of the drug to make up the desired dilution. For instance, to make 5 cc. of agar containing acriflavine, 1: 300,000, 4 cc. of agar plus 1 cc. of 1: 60,000 acriflavine (in water) would be required. Controls were made by adding 1 cc. of sterile water to 4 cc. of agar. These slant agar dilutions were then inoculated from a pure culture of gonococcus (on testicular-infusion agar), and incubated.

Table 4 shows a striking difference between the inhibitory strengths exhibited by acriflavine and the organic silver salts commonly used in the treatment of gonorrhoea. Even proflavine is incomparably stronger than argyrol and protargol. Acriflavine, however, inhibits the development of the gonococcus in the extreme dilution of 1: 300,000, while protargol permits growth even when as concentrated as 1: 500. In considering the low potency of the silver salts, it must be remembered that these experiments were conducted in protein-containing media,

but it is under just these conditions that a drug used clinically in the treatment of gonorrhoea should be efficient. Basing an opinion upon this experiment, there can be no question as to the relative merits of acriflavine and the organic silver salts, and as to which one should be most efficient in controlling the gonococcus. Acriflavine has at least 600 times the strength of protargol against the gonococcus in protein-containing media.

TABLE 4

The dilutions of proflavine, acriflavine and other standard antiseptics which will inhibit the development of the gonococcus in testicular-infusion agar

DILUTION	ACRIFLAVINE	PROFLAVINE	PHENOL	ARGYROL	PROTARGOL
1: 500	0	0	0	0	✱
1: 1,000	0	0	0	✱	✱
1: 10,000	0	0	✱	✱	✱
1: 20,000	0	0	✱	✱	✱
1: 30,000	0	0	✱	✱	✱
1: 50,000	0	0	✱	✱	✱
1: 80,000	0	0	✱	✱	✱
1: 100,000	0	✱	✱	✱	✱
1: 300,000	0	✱	✱	✱	✱
1: 500,000	✱	✱	✱	✱	✱
1: 800,000	✱	✱	✱	✱	✱
1: 1,000,000	✱	✱	✱	✱	✱
Control.....	✱	✱	✱	✱	✱

0 = no growth; ✱ = growth.

CONCLUSIONS

Since acriflavine has been shown (1) to possess the property of diffusibility; since (2) it is antiseptic in urine in higher dilution than any other diffusible dye studied; since (3) it will inhibit the development of the gonococcus in a dilution of at least 1: 300,000 (has at least 600 times the strength of protargol), a trial of this drug in the treatment of gonorrhoea has been experimentally justified.

PART II

BY B. E. HARRELL

The ideal drug for the treatment of gonorrhoea should cause a minimum of injury to the urethral mucous membrane, should be

highly toxic to the gonococcus, and should possess to a high degree the power of penetrating to the deeper structures of the urethra so often involved in this disease. The drugs most often used for this purpose, argyrol and protargol, fulfill these requirements only in part. It was a realization of the shortcomings of our present therapy that these investigations were undertaken.

In view of the recent large advance in our knowledge of the pharmacology of the various dyestuffs, it seemed that our field of greatest therapeutic promise lay in this direction. Considerable work, however, has been done with other substances than acriflavine and these will be taken up in subsequent publications.

When this work was begun we knew of only one dye that possessed to any considerable degree the properties of rapid diffusibility and penetration of the tissues combined with antiseptic power and this dye, one of the halogenated sulphone-phthaleins, was antiseptic to only a slight degree. Accordingly we turned to the commoner dyes that were known to possess antiseptic properties.

The first substance used was gentian violet. This has been the subject of extensive investigation by Churchman (8) who in a series of about 250 strains of bacteria studied, was able to classify them as violet positive and violet negative, as their development was or was not inhibited by the dye. In his technique he adopted the arbitrary dilution of 1:100,000 and found that with this strength of dye his classification corresponded closely to the usual classification of Gram positive and Gram negative. His results with the gonococcus were inconclusive, some strains being inhibited and others not. Churchman showed further that following the intravenous administration of this dye the visible mucous membranes of experimental animals were stained. We repeated this experiment with intravenous and oral administration and found that the genital and intestinal mucous membranes also were stained. We were wary of intravenous injections of the dye in human beings on account of the not uncommon fatalities to laboratory animals following such administration. Oral administration in our cases failed

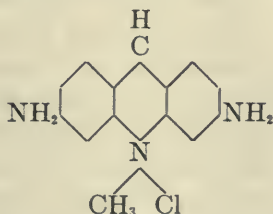
to influence the course of gonorrhoea. Urethral injections of a 1:1000 solution caused a decrease in the discharge, but did not obtain a cure.

We next used basic fuchsin, Fuchsin für Bakterien (Grübler). This substance has been the subject of several papers by May who has shown that a warm 1:1000 solution will kill staphylococci and bacillus coli in five minutes and that even a 1 per cent solution is well borne by the urethra and bladder. Intravenous and oral administration in laboratory animals showed about the same distribution as gentian violet; namely, practically all the mucous membranes. Oral administration in cases of gonorrhoea, however, failed to influence the course of the disease. Urethral injections of a 1:1000 solution were well borne and caused a rapid decrease in the amount of the discharge. In a few cases we were able to obtain a cure in about two weeks.

Urethral injections of methylene blue also were tried. These produced a rapid decrease in the discharge and in a few cases a cure in about two weeks.

Attention was then directed to other dyes possessing the desirable properties of rapid diffusibility and penetration mentioned above, combined with definite antiseptic power; namely, malachite green, brilliant green, proflavine and acriflavine. Of these substances acriflavine quickly demonstrated its value in gonorrhoea.

The compounds brilliant green, proflavine and acriflavine have been the subject of recent frequent publications in the English literature, chiefly by Browning, Gulbransen, Kennaway and Thornton. These authors advocate the use of acriflavine, diamino-methyl-acridinum chloride,



in suppurating wounds and as a prophylactic against suppuration. They have established its high antiseptic value and have shown that this is increased by the presence of serum. In fact, Browning claims that it is ten times as effective in serum as in water. They have also shown that it is not toxic, as they have placed large quantities in the pleural and peritoneal cavities and have injected 300 mgm. intravenously without ill effects. In our experience, we have injected two ounces of a 1 per cent solution into the bladder and have given two grain doses by mouth without symptoms. Another feature brought out by Fleming is its peculiar affinity for leucocytes. This author added the dye to an emulsion of pus cells, removed the cells and found that the remaining fluid showed no trace of the dye and possessed no antiseptic properties.

To determine the degree of diffusibility possessed by the drug, a 1:1000 solution was injected into the urethra and bladder of dogs. The animals were then sacrificed as quickly as possible and blocks taken from these organs for examination. Sections were prepared by the paraffin method and although considerable of the dye was extracted by the fixing reagents, examination showed that it had penetrated to the muscle layers of the urethra and bladder.

The first of this group of dyes used clinically was brilliant green, which Browning has shown will inhibit the growth of staphylococci in water in the extreme dilution of 1:10,000,000. After some preliminary experiments to determine the degree of irritation the dye would produce, we injected a few cubic centimeters of a 1:1,000 solution into the anterior urethra of a case of acute anterior gonorrhoeal urethritis and had the patient retain it five minutes. The injection caused slight stinging and burning. At the end of twenty-four hours the patient had a profuse mucopurulent discharge, but there were no gonococci present microscopically. No organisms were found upon subsequent examinations and the discharge disappeared in forty-eight hours. This patient was seen at intervals of a week for six weeks and has remained well during this time. Further experiments with this dye, however, have shown that this strength

was too irritating for general use and that weaker dilutions did not give the desired results.

TECHNIQUE

Urethral injections of acriflavine cause slight smarting which persists for an hour or more. Patients who have had previous treatment with protargol tell us, however, that it is decidedly less than that caused by the silver salt. The smarting has never been severe and we have had no patient object to the treatment. We have used dilutions varying from 1:2,000 to 1:100, and have found the 1:1,000 most satisfactory; it is just as efficient as the more concentrated solutions and the smarting is less, in fact, with this strength it is almost negligible. We have had two cases of retention following the use of a 1 per cent solution. These cases complained of no pain except that caused by the inability to void. There was evidently no stricture formation as they were catheterized without difficulty and the symptoms promptly disappeared on discontinuing treatment. There have been no complications following the use of a 1:1,000 solution.

In the anterior cases we have injected about 3 cc. of a 1:1,000 solution into the anterior urethra the patient retaining it for five minutes. In the posterior cases we have injected 15 to 30 cc. through into the bladder, distending the urethra and having the patient retain the dye in the urethra for five minutes and in the bladder till the next voiding. Injections should be given twice a day until all organisms have disappeared from the discharge and then once a day until the patient is considered well. All our results have been controlled by daily examination of smears from the urethral discharge and of the urine voided in three glasses.

RESULTS

We have frequently had the organisms disappear from the discharge following a single injection and not return during the subsequent course of the disease. In the majority of cases they have disappeared after two or three injections. In a few cases

they have disappeared after one or two injections and have been found again later, but have soon disappeared under continued treatment.

The discharge is markedly decreased from the beginning, very quickly becoming thin and mucoid in character. It then gradually becomes less until about the fifth day it has usually disappeared altogether. In a few of the more resistant cases we have noticed the fragmentation of the leucocytes mentioned by Browning.

TABLE 5

	DURATION OF DISEASE	DURATION OF TREATMENT IN DAYS	NUMBER OF TREATMENTS
1	3 days	3	3
2	2 months	3	4
3	4 months	2	2
4	5 months	3	3
5	4 days	5	5
6	6 days	5	5
7	8 months	6	7
8	2 weeks	5	8
9	2 months	5	8
10	?	11	13
11	1 day	7	7
12	2 years	7	7
13	3 weeks	16	16
14	4 months	12	13
15	10 days	14	16
Average.....		$6\frac{14}{15}$	$7\frac{12}{15}$

In cases of anterior and posterior urethritis we have found that the posterior infection usually improves before the anterior, in fact, it is usual for the urine voided in three glasses to be cloudy in the first and clear in the second and third. The trigonal inflammation also quickly subsides. Cases with frequency and nycturia have frequently had these symptoms entirely relieved by a single injection, nearly always by two or three.

Some of the dye evidently remains in the urethra for a considerable time. The discharge at the end of twenty-four hours is still stained a brilliant yellow and microscopically many of the leucocytes are well stained. The urine is definitely yellow and is fluorescent even at the end of thirty-six hours.

The cases in the above table, though some of them gave a history of gonorrhoea lasting from a few weeks to two years, have all had a purulent discharge showing intracellular diplococci when seen by us. Many of them had been receiving treatment since the onset of the disease. One case not included in the list gave a history of gonorrhoea lasting for four years and had been receiving treatment regularly for more than a year. This case cleared up very quickly, but is not included as this was one of our earliest cases and other substances beside flavine were used in his treatment, though we believe the final result was obtained with this drug.

We have had recurrences as is the rule with any form of treatment. We have not resumed treatment in these cases till they had developed the maximum of immunity, usually in five to seven days. Treatment at the end of this time has usually given prompt results.

A striking feature of this form of therapy is that in many cases the dye acts almost as a specific, while in an occasional one it seems without any effect whatever. Such cases are evidently not very common, however, as in the considerable number that we have treated we have found only four of this class. Two of these responded at once to injections of protargol. In the third case the discharge was much decreased by acriflavine, but we could not obtain a cure. This patient was entirely relieved by a single injection of a member of the aromatic series with which we were working and has remained well. In the fourth case we have not yet obtained a cure with either acriflavine, protargol, or with potassium permanganate. Whether this condition is due to an especially resistant strain of the gonococcus or to some other undetermined cause, we are not able to say.

We have used acriflavine in a large number of cases but include in the above table only those that we have been able to follow for several weeks after treatment was discontinued. We realize that this is a small number to report but the uncertainties of military service lead us to do so at this time. We have found several other substances that have considerable value in gonor-

rhoea and further investigations will be carried out at the earliest opportunity.

So far we have not been able to obtain acriflavine in this country. Our supply for this work was obtained from the Boots Pure Drug Company, Ltd., Nottingham, England.

Case 1. This patient came in complaining of painful urination of twenty-four hours' duration, coming on three days after exposure. Examination showed a slight purulent urethral discharge which on smear showed numerous intracellular diplococci. Glass 1 was cloudy, glasses 2 and 3 clear. He was given an anterior injection of flavine 1:250. When seen again at the end of twenty-four hours his symptoms had entirely disappeared, there was no discharge at the meatus and scrapings from the urethra showed no organisms; the urine was clear in all three glasses. This patient was given another injection at this time and another twenty-four hours later, or three injections in all. He did not complain of pain either during or after the injections. He was seen again after three days and again ten days later, his examination being entirely negative on each occasion.

Of course, it is not unusual for the disease to be aborted by other methods of treatment, but the following cases will show somewhat similar results with cases of longer duration.

Case 2. This patient gave a history of gonorrhoea of two months' duration, during which time he had been under constant treatment both by injections of protargol and irrigations of potassium permanganate. Examination showed a profuse, purulent urethral discharge which on smear showed numerous intracellular diplococci, urine cloudy in all three glasses. He was given a posterior injection of flavine 1:250. At the end of twenty-four hours there was still a slight discharge, there were no organisms present, the urine was cloudy in the first glass, clear in the second and third. At the end of forty hours or on the morning of the third day, there was only a slight moisture at the meatus, no organisms present, the urine clear in all three glasses. He was given a third injection at this time and a fourth in the afternoon or at the end of forty-eight hours. He states that the flavine caused slight smarting, but distinctly less than the protargol that he had been using. This patient has been seen every few days for three months and has remained entirely well during this time.

Case 3. Gave a history of gonorrhoea of four months' duration with intermittent treatment with protargol since onset. Examination showed a moderate purulent discharge which showed numerous organisms on smear. Glass 1 was cloudy, glasses 2 and 3 clear. He was given an anterior injection of flavine 1:250. On the morning of the second day his condition was the same except that there were no organisms in the discharge. He was given another anterior injection of the same strength. On the afternoon of the second day, or at the end of twenty-four hours there was a slight mucoid discharge at the meatus, no organisms on smear, urine slightly cloudy in the first glass. We were anxious to know just how quickly a cure could be obtained so he was given only the two treatments. Three days later there was no discharge and the urine was clear in all three glasses. This patient was seen at intervals of a week for a month and has remained well.

Case 4. Had had gonorrhoea for five months with intermittent treatment with protargol. Examination showed a slight purulent discharge which showed a good many organisms on smear, glass 1 cloudy, glasses 2 and 3 clear. He was given a posterior injection of flavine 1:2000. After twenty-four hours there was no discharge, no organisms in scrapings from the urethra, urine still hazy in the first glass. He was given flavine 1:1000 anteriorly. After forty-eight hours the findings were the same so was given another injection of 1:1000, or three injections in all. No further treatment was given and the patient has remained well.

Case 5. Had a gonorrhoea of four days' duration. Examination showed a slight discharge showing numerous organisms on smear, urine cloudy in all three glasses. He was given a posterior injection of flavine 1:250. On the second day there was still a slight discharge, no organisms on smear, urine cloudy in the first glass, clear in the second and third. He was given one injection a day for five days. At the end of this time there was no discharge, the urine showed a few shreds in the first glass, glasses 2 and 3 clear.

Case 6. Had had gonorrhoea for six days. Examination showed a purulent discharge containing numerous intracellular diplococci, glass 1 cloudy, glasses 2 and 3 not obtained. He was given an anterior injection of flavine 1:1000. On the second day there was still a slight discharge, but no organisms on smear, glasses 1 and 2 cloudy. Was given flavine 1:1000 posteriorly. On the third day there was a slight moisture at the meatus, no organisms on smear, glass 1 hazy,

glasses 2 and 3 clear. The condition remained the same while a total of five injections in as many days were given, when treatment was discontinued. Subsequent examinations showed him to be entirely well.

Case 7. This patient gave a history of gonorrhoea of eight months' duration. Examination showed a moderate purulent discharge showing large numbers of organisms on smear, urine cloudy in all three glasses. He was given a posterior injection of flavine 1:1000. On the second day the discharge was still present, but without organisms, urine cloudy in the first glass, clear in the second and third. On this day was given two injections. From this time on posterior injections of 1:2000 were used once a day. On the fourth day the discharge was thin and mucoid in character. Treatment was discontinued on the sixth day. At this time there was still a slight moisture at the meatus and a few shreds in the first glass. Ten days later there was still an occasional shred in the first glass, examination otherwise negative. This patient has remained well since this time.

This case is a good example of the rapidity with which the posterior urethritis is relieved.

Case 8. Had had gonorrhoea for two weeks. Examination showed a profuse discharge, many organisms on smear, urine cloudy in all three glasses. He was given a posterior injection of flavine 1:1000. On the second day there was a slight discharge, no organisms on smear, urine cloudy in all three glasses. From this time on was given two injections per day till the fourth day. On the fifth day was given a single injection of 1:2,000. At this time there was still a slight moisture at the meatus and the urine was hazy in the first glass. Patient has remained well.

Case 9. Had a gonorrhoea of two months' duration. Examination showed a slight discharge, a few organisms on smear, urine cloudy in all three glasses. He was given a posterior injection of flavine 1:250. On the morning of the second day his condition was unchanged and was given flavine 1:500. At the afternoon examination there was no discharge, no organisms on smear, urine still cloudy in all three glasses. Following this he received two injections per day till the fifth day when he was given a single injection of 1:1000 and treatment discontinued. The urine became clear in glasses 2 and 3 on the fourth day, clear in all three glasses on the fifth day. This patient has been seen at intervals for three months, but has remained well.

Case 10. This was the only hospital case in the series. His mental condition made it impossible to obtain a history and only rarely could we obtain a specimen of urine. Examination showed a fairly profuse discharge showing numerous intracellular diplococci on smear. He was given a posterior injection of flavine 1:1000. On the second day there was a slight discharge, no organisms on smear. On this day was given two treatments of 1:1000 and for the remainder of the time one treatment of 1:2000 per day till thirteen injections had been given in all. On the third day the discharge was thin and mucoid in character, urine cloudy in glass 1 clear in glasses 2 and 3. On the fifth day there was no discharge and on the ninth the urine was clear in all three glasses. Treatment was discontinued on the tenth day and the patient has remained well.

Case 11. This patient gave a history of gonorrhoea of twenty-four hours' duration and complained of considerable burning on urination. Examination showed a thick creamy discharge, numerous organisms on smear, glass 1 cloudy, glasses 2 and 3 clear. He was given an anterior injection of flavine 1:250. On the next day there was no burning on urination, an occasional organism on smear, the urine remained the same. Injections of the same strength were given once per day for seven days. On the fourth day there was very little discharge, no organisms on smear. On the fifth day there was an increase in the discharge, a few organisms on smear, some burning on urination; glasses 1, 2 and 3 cloudy. These promptly cleared up under posterior injections and on the seventh day treatment was discontinued. At this time there was no discharge, no organisms on smear, urine hazy in the first glass. Patient has remained well.

Case 12. Had had gonorrhoea for two years with intermittent treatment with protargol. Examination showed a moderate discharge, a few organisms on smear, urine cloudy in all three glasses. This patient was getting up five times at night to void. He was given a posterior injection of flavine 1:1000 and received the same treatment each day thereafter for seven days. Following the first treatment he got up only once at night and following the second not at all. On the fourth day there was only a slight discharge and all organisms had disappeared. On the fifth day there was no discharge, urine hazy in the first glass, clear in the second and third. Treatment was discontinued on the seventh day and the patient has remained well.

Case 13. Gave a history of gonorrhoea for three weeks without treatment. Examination showed a slight discharge, no organisms on

smear, urine cloudy in all three glasses. He was given a posterior injection of flavine 1:1000 and the same treatment once each day thereafter. On the second day there was a slight discharge, no organisms on smear, urine still cloudy in all three glasses. On the third day the discharge had disappeared. On the seventh day the urine was hazy in the first glass, clear in the second and third. Treatment was discontinued.

Three days later patient returned in the same condition as when first seen, namely, with a slight discharge, a few organisms, urine cloudy in all three glasses. The organisms disappeared after a single injection and the discharge after two. After three treatments organisms were again found in the discharge, but disappeared two days later, at which time also the urine became clear in glasses 2 and 3. On the sixteenth day there was no discharge and the urine showed only an occasional shred in the first glass. Treatment was discontinued and the patient has remained well.

Case 14. Gave a history of gonorrhoea for four months with almost continuous treatment with protargol. Examination showed a profuse purulent discharge, numerous organisms on smear, urine cloudy in all three glasses. He was given a posterior injection of flavine 1:100. On the second day there was a slight discharge, a few organisms, glasses 2 and 3 clear. He received two injections on this day and another on the third day. Following this he had complete retention which necessitated catheterization, though he did not complain of any pain except that caused by the inability to void. There was evidently no stricture formation as a no. 20 F catheter was introduced without difficulty. Treatment was not resumed till four days later when the dysuria had entirely disappeared. At this time he again had a thick purulent discharge with numerous organisms on smear, the urine, however, was clear in the second and third glasses. The organisms disappeared after two injections of flavine 1:1000 and the discharge was decreased in amount. A slight moisture persisted at the meatus till after treatment was discontinued. On the twelfth day this moisture was still present, the urine showed an occasional shred in the first glass, second and third glasses clear. Treatment was discontinued and the patient has remained well.

We have had one other case of retention. This one also was catheterized without difficulty and the dysuria cleared up in about four days. This patient did not return for treatment until

he was well and could not be traced, so is not included in our list. This retention was probably due to oedema or spasm of the vesical orifice as there were no persistent pathological changes.

Case 15. Gave a history of gonorrhoea of ten days' duration without treatment. Examination showed a moderate discharge, numerous intracellular diplococci on smear, urine cloudy in all three glasses. He received a posterior injection of flavine 1:1000 at this time, two injections on the second and fourth days, and one injection per day thereafter. On the second day the urine was clear in the second and third glasses, and the discharge much decreased. On the fourth day the organisms had disappeared, but the urine was again cloudy in glasses 2 and 3. On the fifth day the urine was only hazy in the first glass, clear in the second and third. The patient's condition remained the same till the fourteenth day when the discharge had disappeared and the urine was clear in all three glasses. Treatment was discontinued and the patient has remained well.

CONCLUSIONS

1. Acriflavine will inhibit the development of the gonococcus in a protein-containing media in a dilution of 1:300,000. (Has 600 times the strength of protargol.)

2. It will penetrate through the submucosa of the urethra and bladder.

3. It is non-toxic and only slightly irritating to the urethral mucous membranes.

4. The average duration of a gonorrhoea under this treatment is distinctly less than with the usual methods.

5. In an occasional case it seems without effect upon the course of the disease.

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URINARY ANTISEPSIS—THE SECRETION OF ANTISEPTIC URINE FOLLOWING THE INTRAVENOUS ADMINISTRATION OF AN ORGANO-MERCURY PHTHALEIN DERIVATIVE

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In previous publications (Davis, Davis and White) the need of an efficient internal urinary antiseptic has been discussed, and the experiments relative to the synthesis of such a compound have been described. By the term "internal urinary antiseptic" is meant a drug which, administered by mouth or intravenously, will render the urine antiseptic for a definite period of time, regardless of the reaction of the latter, and without injury to the patient. The ideal compound for this purpose must be chemically stable and relatively non-toxic and non-irritating; must be antiseptic in high dilution (in urine as well as in water); and, in order that minimal dosage may be efficiently and safely administered, must be eliminated in high percentage by the kidney, as is, for example, phenolsulphonphthalein. Clinically, there is no such drug known. The present paper is a discussion of the chemistry, antiseptic properties, toxicity and excretion of chlor-mercury fluorescein, a synthetic compound which we have shown experimentally to possess the properties enumerated above; that is, *this compound, administered intravenously in minute doses, will cause the secretion of antiseptic urine, for a definite period of time, without injury to the animal.*

The investigation was begun with phenolsulphonphthalein, and experiments concerning the antiseptic strength and the excretion of various related compounds were carried on, with the object of establishing a relationship between chemical structure and "renal affinity." More than two hundred compounds have been studied, with the following previously published conclusions:

1. The property possessed by phenolsulphonphthalein, by virtue of which it is so rapidly eliminated by the kidney, is by no means limited to this compound, for several other more or less closely related compounds show the same striking "renal affinity."

2. Compounds of the xanthone class, that is, phthaleins (though not necessarily sulphonphthaleins) in which there is an oxygen atom linking the two phenol groups, show a similar remarkable "renal affinity."

3. The bromination of these compounds, both sulphonphthaleins and xanthenes, interferes with their excretion.

4. Numerous actively germicidal compounds lose their strength (owing to an as yet unexplained cause) when simply diluted with urine in a test tube. The value of every drug used for the purpose of urinary antisepsis ought therefore to be questioned until its antiseptic strength *in urine* has been experimentally demonstrated.

5. It has been possible to establish a certain relationship between chemical structure and renal excretion, and to predict, with a reasonable amount of accuracy, which drugs will and which will not be rapidly excreted.

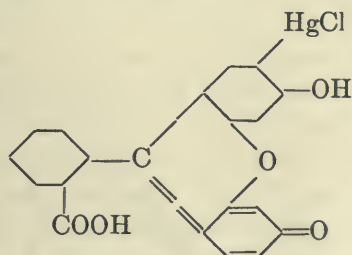
6. The synthesis of germicidal compounds, very closely related to the types excreted, has been accomplished, and one of these germicidal compounds (rhodamin) was excreted and would have been successful but for the interfering action of the urine.

The properties of chlor-mercury fluorescein were not discovered accidentally. The compound was logically synthesized according to the rules stated above, that is, by the combination of an antiseptic agent with a molecule containing a certain definite chemical structure previously shown to possess "renal affinity." The resulting molecule thus possesses two functions, one of which acts to localize and concentrate in one portion of the body (the kidney), and the other exerts an antiseptic action. This feature (the rapid localization of the antiseptic in the urine) is of the utmost importance, for it is thus made possible to produce an efficient concentration of the drug in the urine by the use of dosage so minute that the danger from toxicity has been experimentally

eliminated, in spite of the mercury content. Were it not for the localizing tendency possessed by this drug, and were it therefore necessary to produce a concentration throughout the entire body equal to that in the urine, the question of toxicity would perhaps rule out a consideration of the drug for clinical purposes.

CHEMISTRY

Chlor-mercury fluorescein is formed by the introduction of one atom of mercury into the fluorescein molecule. A description of the preparation of the material and its properties, as well as that of other organo-mercury derivatives of phthaleins and sulphophthaleins, which have been prepared and investigated in this laboratory, and rejected through lack of one or more of the above listed requirements, will be published in an appropriate chemical journal. It may be said here that the substance is probably represented by the formula,



the *position* of the mercury here given being probable, though not yet definitely established.

The substance is an orange powder, identical in appearance with fluorescein. It is readily and completely soluble in dilute sodium hydroxide or sodium carbonate, thus showing that the mercury is present in *non-ionic* form. The solution of the sodium salt has practically the same color and fluorescence as fluorescein itself. This solution is entirely stable, and has been kept for months without deterioration. The formula given requires a mercury content of 35.37 per cent, and the analysis of the substance gives results agreeing very closely with this theoretical figure.

In this connection it is interesting to note that organo-mercury derivatives of phthaleins, including fluorescein, have been investigated with regard to their therapeutic action in trypanosome infections, by Hahn and Kostenbader and by Klages and Schreiber. It is evident from the publications of these writers that the same set of substances was used in both investigations. These authors, however, give no description of the method of preparation, nor is any mention of them to be found in the chemical literature. However, the mercury content of their fluorescein derivatives (one 25 per cent and another 50 per cent) does not agree with any conceivable formula for an organo-mercury derivative of the dye. It therefore seems probable that these authors were not dealing with pure, definite substances. In any case, our drug, as indicated by its mercury content, is different from theirs, and appears to be a definite chemical individual.

ANTISEPTIC PROPERTIES IN VITRO

As has been previously mentioned, the possession of antiseptic properties by a drug when diluted in water is no indication whatever of its antiseptic value when diluted in urine. In fact, most of our compounds which were germicidal in high dilution in water lost this property when diluted in urine in a test tube, and even permitted the growth of organisms in urine when in relatively high concentration. In determining the antiseptic and germicidal value of chlor-mercury fluorescein, it was therefore desirable to make the various dilutions with voided urine, since any drug for our purpose would be useless unless effective in this medium. Furthermore, it was desirable to try out the drug in both acid and alkaline urines, since the ideal drug should be efficient regardless of the urinary reaction. The necessity for an acid urine is the most serious obstacle to the efficiency of urotropin.

Reaction of urine. In order to have available each day urine of definite acid and alkaline reaction, it was necessary to titrate specimens of voided urine with tenth normal sodium hydroxide and tenth normal hydrochloric acid until definite degrees of hydrogen ion concentration were reached, as determined by the

colorimetric method; that is, by comparison with a standard hydrogen ion scale made up with solution of buffer salts colored by the sulphonphthalein series of indicators. (See publications of Clark and Lubs, and Shohl and Janney.) On the acid side of the scale it was arbitrarily decided to use urine titrated to $p_H 6.0$ (corresponding to 0.000001 N acid), which Henderson and Palmer have shown to be the average reaction of normal urine. In order to obtain alkaline urine, a sample of the same specimen was titrated to $p_H 8.0$, an end-point arbitrarily chosen so that the reaction of the specimens of urine used from day to day would not vary.

Technique. Dilutions of the drug were made in sterile test tubes, using acid urine for one series of dilutions and alkaline urine for another. Each dilution was inoculated with one loop of a twenty-four hour broth culture of the colon bacillus in one series of experiments, and with the staphylococcus aureus in another. After an incubation period of twenty-four hours (sufficient time to permit either growth or death of the organism), 0.1 cc. was transferred from each tube to melted agar and plated. Those plates which remained sterile, or in which only a few colonies developed, proved that the corresponding tubes contained an inhibitory concentration of the drug. Those plates in which the colonies were too numerous to be counted (designated in the tables by the infinity sign, ∞) proved that the concentration of the drug had been insufficient to prevent growth of the organism.

Antiseptic strength. Table 1 shows that chlor-mercury fluorescein is more effective in acid than in alkaline urine, in the case of both the colon bacillus and the staphylococcus. Even in alkaline urine, however, the development of both organisms was inhibited by a dilution of 1:10,000. (Carbolic acid, in urine, permits a growth of the colon bacillus in a concentration of 1:1,000.) The question mark in table 1 indicates an inconstancy of results when the experiment was repeated several times. For instance, in a dilution of 1:30,000, the drug killed the colon bacillus on some occasions, and on other occasions permitted growth. The variable factor here was not determined, although it seems likely

TABLE 1

The antiseptic strength of chlor-mercury fluorescein diluted in voided human urine

DILUTION OF DRUG IN URINE	COLON BACILLUS		STAPHYLOCOCCUS AUREUS	
	Acid urine (p _H , 6.0)	Alkaline urine (p _H , 8.0)	Acid urine (p _H , 6.0)	Alkaline urine (p _H , 8.0)
1: 1,000	0	0	0	0
1: 10,000	0	0	0	0
1: 20,000	0	∞	0	10,000 %
1: 30,000	?	∞	∞	∞
1: 40,000	∞	∞	∞	∞
1: 50,000	∞	∞	∞	∞
1: 100,000	∞	∞	∞	∞
Control of drug-free urine.....	∞	∞	∞	∞

Each dilution was inoculated with one loop of a twenty-four hour broth culture and incubated for twenty-four hours after which 0.1 cc. was transferred to a tube of melted agar, and plated. Columns indicate approximate number of colonies which developed in plates.

0 = no growth; ∞ = infinite number of colonies; 10,000 % = approximately 10,000 colonies (indicates that the organisms were inhibited, but not killed, during twenty-four hours).

TABLE 2

The germicidal strength of chlor-mercury fluorescein diluted in voided human urine

DILUTION OF DRUG IN URINE	COLON BACILLUS		STAPHYLOCOCCUS AUREUS	
	Acid urine (p _H , 6.0)	Alkaline urine (p _H , 8.0)	Acid urine (p _H , 6.0)	Alkaline urine (p _H , 8.0)
1: 1000	0	0	0	0
1: 10,000	0	0	0	0
1: 20,000	1,000 %	10,000 %	0	10,000 %
1: 30,000	10,000 %	10,000 %	50 %	10,000 %
1: 40,000	10,000 %	10,000 %	10,000 %	10,000 %
1: 50,000	10,000 %	10,000 %	10,000 %	10,000 %
Control of drug-free urine.....	10,000 %	10,000 %	10,000 %	10,000 %

Each dilution was inoculated with one loop of a twenty-four hour broth culture, and incubated for one hour, after which 0.1 cc. was transferred to a tube of melted agar, and plated. Columns indicate approximate number of colonies which developed in plates.

0 = no growth; 10,000 % = approximately 10,000 colonies.

that the discrepancy was due to a variation in the constituents of the urine, other factors being constant. Less extreme dilutions exhibited no such inconstancy.

Germicidal strength. The technique for these experiments was identical with that for the antiseptic test, except that the inoculated dilutions were incubated for only one hour (instead of twenty-four) before 0.1 cc. was removed and plated. The surprising feature shown in table 2 is that the drug is almost as effective in one hour as in twenty-four. In either acid or alkaline urine, in a dilution of 1:10,000, chlor-mercury fluorescein will kill the colon bacillus or the staphylococcus aureus in one hour. In water, in the same time, the same drug will kill the colon bacillus in a dilution greater than 1:100,000, which shows how much more difficult the problem of antiseptics is rendered by the presence of urine.

EXCRETION

The excretion of chlor-mercury fluorescein must be considered in two phases—the excretion of the dye and the excretion of mercury. Although the mercury in the drug is a part of the fluorescein molecule, being actually bound to a carbon atom of a benzene ring, one must take into account the possibility that the mercury may be split out of the molecule by processes in the organism, and that the products of the cleavage, fluorescein and mercury in some new form of combination, may not be excreted in equivalent amounts. For this reason the colorimetric estimation of the amount of the drug in the urine gives no certain information about the amount of mercury present. It was therefore necessary to make a quantitative determination of mercury in the urine, as well as the colorimetric estimation of the dye output. The findings in these two directions will be discussed separately.

Excretion of the dye. The appearance of a strongly fluorescent substance in the urine may indicate unchanged chlor-mercury fluorescein or mercury-free fluorescein. The rapidity of the appearance is as great as, if not greater than, that of phenol-sulphonphthalein. Following the intravenous administration of

small doses (5 to 10 mgm.) to dogs and rabbits, fluorescence appears in the urine within three or four minutes, and with larger doses (100 mgm.) we have noted its appearance through a catheter as early as *eighty seconds* after injection. By far the greater part of a 10 mgm. dose has been eliminated after 1 hour, although in some instances minute traces may be detected after several hours. Although the colorimetric estimation of fluorescent substances is rather inaccurate, there can be no doubt that *more than 70 per cent* of a 10 mgm. dose is excreted during the first hour; some of the readings were as high as 90 per cent.

The affinity of the kidneys for this compound, and for phenol-sulphonphthalein and other chemically related substances, is astounding when one considers the extreme dilution that a 5 mgm. dose undergoes when injected into the blood stream of an animal weighing several million times as much, yet the drug (or the fluorescein portion of it) passes through the kidney tubules and pelvis, down the ureter, across the bladder and through a catheter in less than two minutes.

The localization of fluorescent substance in the kidney was demonstrated by autopsies done upon dogs less than one hour after the intravenous injection of large doses. In these cases section of the kidney always showed an intense greenish coloration, while the other organs had normal color. This coloration of the kidney, as shown by autopsies done upon dogs four or five hours after injection, is only transient, and disappears after the excretion of fluorescent substance has ceased.

Excretion of mercury. Various methods for the quantitative determination of mercury were considered, that of Lomholt and Christiansen being chosen as offering the maximum of convenience and reliability. In order to test the method, determinations were run upon mercury-free urine and upon urine to which known amounts of chlor-mercury fluorescein had been added. After a few trials accurate results were obtained.

The results of the analysis of urine from animals that had been given doses of the drug large enough to produce antiseptic urine are given in table 3. These results show that the excretion of mercury is by no means parallel to that of the dye. Whereas

at least 70 per cent of the dye is excreted by rabbits within 1 hour, only one-sixth to one-half of the mercury is found in the urine within twenty-four hours. The one experiment on a dog showed an excretion of only 19 per cent of the mercury within twenty-four hours, and men excreted an even smaller part of the metal. Although the figures given do not permit any definite conclusions as to the effect of the size of the animal or size of dose on the percentage of mercury excreted, the small mercury output as compared with the large fluorescein output indicates a cleavage of chlor-mercury fluorescein within the organism.

TABLE 3

Excretion of mercury in the urine after injection of small doses of chlor-mercury fluorescein

ANIMAL	DOSE OF CHLOR-MERCURY FLUORESCIN	MERCURY IN URINE				TOTAL Hg EXCRETED IN 24 HOURS	Hg EXCRETED IN 24 HOURS
		After 1 hour	After 2 hours	After 3 hours	After 24 hours		
	mgm.	mgm.	mgm.	mgm.	mgm.	mgm.	per cent
Rabbit 48....	5 (= 1.7 mgm. Hg)	0.5			0.2	0.7	41
Rabbit 49....	5 (= 1.7 mgm. Hg)		0.2		0.1	0.3	18
Rabbit 51....	5 (= 1.7 mgm. Hg)			0.5	0.1	0.6	35
Rabbit 54....	5 (= 1.7 mgm. Hg)				0.4	0.4	23
Dog 22.....	25 (= 8.7 mgm. Hg)		0.6	0.5	0.6	1.7	20
Patient I....	20 (= 7.0 mgm. Hg)				0.8	0.8	11
Patient II....	10 (= 3.5 mgm. Hg)				0.3	0.3	8

When one considers the minute amount of mercury present in the twenty-four hour urine from a man given 10 or 20 mgm. of the drug—a dose that will be shown below to produce definitely antiseptic urine—the possibility is suggested that the antiseptic substance in the urine is not chlor-mercury fluorescein or any other mercury compound, but that under the influence of the drug the kidney secretes some second substance that produces the antiseptis. Color is lent this explanation by the observations of Davis and Hain that normal dog or rabbit urine is frequently antiseptic.

TECHNIQUE

Administration of drug. In determining toxicity, rate of elimination and urinary antiseptics dogs and rabbits were used. In general, the method of procedure was to obtain the urine by catheterization just before administration of the drug, and again at intervals of one, three and five hours afterward. The drug was used as the sodium salt, in 1 per cent solution, given intravenously. Although we carried out a few experiments in which the drug was given by mouth and intramuscularly, the investigation was interrupted before the effectiveness of these methods of administration could be determined.

Catheterization. Male animals were used, and all catheterizations done with aseptic precautions, after washing the penis and irrigating the anterior urethra with 1:10,000 bichloride. The urethra of the male rabbit is easily catheterized with a small soft, rubber catheter. For the dogs, a small, stiff, olive-tipped, gum catheter was found to be most satisfactory. All catheters were sterilized by boiling, and the urine collected in sterile test tubes. Urine obtained from a normal animal by this procedure was almost invariably sterile, even after incubation.

Bacteriology. The object was to determine the antiseptic value (not the germicidal value) of each specimen of urine, that is, to determine whether or not the urine would act as a favorable culture medium. The method of procedure was to inoculate each sample of urine with one loop of a twenty-four hour culture of the colon bacillus, incubate for twenty-four hours and at the end of that time, plate a definite volume (0.1 cc.) of the inoculated, incubated urine. This method, dependent upon observing the number of colonies in an agar plate, accurately determines whether or not the organism has developed or died during the twenty-four hour incubation period, and is not open to fallacy as is the method of simply inspecting the incubated urine for cloudiness, or the method dependent upon determining change in reaction. Each experiment was accurately controlled by a specimen of urine obtained just before administration of the drug, and inoculated and subjected to identically the same conditions

as those specimens obtained at intervals after injection. It should be pointed out here that, as shown by Davis and Hain, normal dog and rabbit urine sometimes acts as an unfavorable culture medium for the colon bacillus, and may even kill this organism after several hours. We have never observed a failure of the organisms to grow in normal human urine. On account of this fact it was necessary to run with each experiment a control of urine obtained just before administration of the drug. All experiments not so controlled were discarded.

In most of the experiments only the colon bacillus was used, while in others the antiseptic action of the urine toward the staphylococcus aureus and staphylococcus albus was also determined. In the latter case, each specimen of urine (including one specimen obtained before the administration of the drug, and one, two or three specimens obtained at intervals afterward) was divided into four equal parts (each containing 2 cc.) in sterile test tubes. Of these four portions, three were inoculated with one loop of a twenty-four hour broth culture of colon bacillus, staphylococcus aureus and staphylococcus albus respectively, the remaining one was not inoculated at all, and the four were then incubated at 37°C. At the end of twenty-four hours, 0.1 cc. was transferred from each tube of urine with a sterile capillary pipette to melted agar and plated. The plates were inspected after twenty-four hours and after forty-eight hours. A plate showing no colonies, or very few colonies, (less than 100) proved that particular specimen of urine to be antiseptic, while the presence of countless numbers of colonies (designated in the tables by the infinity sign, ∞) showed that the organism had grown and developed and that the urine had acted as a favorable culture medium. Since 0.1 cc. of urine, plated from a 2 cc sample *immediately* after inoculation with one loop of a twenty-four hour broth culture of the colon bacillus, will show several thousand colonies, there can be no question that the presence of only one hundred colonies, or less, in a plate containing 0.1 cc. of inoculated, *incubated* urine, proves that specimen of urine to be antiseptic. It was advisable to incubate a portion of uninoculated urine from each specimen, simply to prove that that particular specimen

was sterile, so that, in case growth should take place in any of the inoculated portions, it would be certain that the growth was due to the inoculating organism and not to contamination.

SECRETION OF ANTISEPTIC URINE

Rabbits. With rabbits (see table 4) we were able consistently to produce antiseptic urine for a period of at least one hour following the intravenous injection of 5 mgm. of the drug. Out of seven rabbits receiving 5 mgm. (about 2.5 mgm. per kilogram) the urine obtained before injection acted as a favorable culture medium in all, while the urine obtained one hour after injection, in all cases but one, killed the colon bacillus. The urine of one rabbit, obtained two hours after injection, still retained its antiseptic action. In two instances, the specimen of urine obtained three hours after injection was still distinctly inhibitory, although not all of the organisms were killed; and one of these rabbits (38), catheterized at intervals of one, three and five hours, nicely shows the transient effect of the drug in the urine; that is, after one hour the urine was germicidal, after three hours, inhibitory, and after five hours it had again become a favorable culture medium. The specimens of urine from rabbit 79, which was given 20 mgm., were inoculated not only with the colon bacillus but also with staphylococcus aureus and staphylococcus albus. This mixed culture was killed in the two-hour specimen, but was permitted to grow in the five-hour specimen. The urine of rabbit 35 (after 15 mgm.) was the only one to retain its antiseptic action for as long as five hours. A dose smaller than 5 mgm. was ineffective. Of three rabbits receiving 2.5 mgm. each, the urine of one (36) was inhibitory, while the other two permitted growth.

In order to demonstrate the necessity of the *fluorescein* portion of the molecule in causing the action in the urinary tract, a rabbit was given, intravenously, an amount of mercuric chloride (4.7 mgm.) containing the same amount of mercury as does 10 mgm. of chlor-mercury fluorescein, which is twice the antiseptis-producing dose. The specimens of urine obtained one and three hours after the injection of mercuric chloride both permitted growth of the colon bacillus.

Dogs. Regardless of the size of the dog, a 5 mgm. dose was effective in producing antiseptic urine. It is important to note that *this was the same dose as was required in rabbits.* Of the dogs listed in table 5, each of which received 5 mgm. intrave-

TABLE 4

The secretion of antiseptic urine by rabbits following the intravenous administration of small doses of chlor-mercury fluorescein

RABBIT	DOSE	APPAR- ENT EFFECT UPON ANIMAL	ALBU- MIN	CASTS	NUMBER OF COLONIES WHICH DEVELOPED IN AGAR PLATE CONTAINING 0.1 CC. OF URINE WHICH HAD PREVIOUSLY BEEN INOCULATED AND INCUBATED FOR 24 HOURS				
					Urine obtained just before injection	Urine obtained 1 hour after injection	Urine obtained 2 hours after injection	Urine obtained 3 hours after injection	Urine obtained 5 hours after injection
	<i>mgm.</i>								
79	20	None	+	?	∞	0	0		∞
35	15	None	—	None	∞	0			0
28	10	None	—	None	∞	0			
38	5	None	—	None	∞	0		500 %	∞
35	5	None	—	None	∞	0			
28	5	None	—	None	∞	0			
48	5	None	—	None	∞	0			
49	5	None	—	None	∞		0		
51	5	None	—	None	∞			500 %	
38	5	None	—	None	∞	∞			
36	2.5	None	—	None	∞	50 %			
28	2.5	None	—	None	∞	∞			
38	2.5	None	—	None	∞	∞			

* Transient.

All specimens of urine (excepting those of rabbit 79) were inoculated with one loop of a twenty-four hour broth culture of the colon bacillus. The specimens from rabbit 79 were inoculated with colon bacillus and also with staphylococcus aureus and staphylococcus albus.

Examinations for casts and albumin were made on the first or second day following the administration of the drug.

50 % = Approximately 50 colonies.

nously, the urine obtained before injection permitted growth of the colon bacillus, while the plates poured from the specimens of urine obtained one hour later with only one exception were sterile. This exception (dog 21) may be accounted for by the fact that at the time there was a marked diuresis, and hence a

dilution of the drug. Each of the dogs, excepting dog 20, weighed about 10 kgm. This one dog was unusually large, weighing 25 kgm., yet the 5 mgm. dose was effective, just as with the smaller dogs. A five-hour specimen obtained in this instance permitted growth and therefore demonstrates the transient nature of the antiseptic action.

Several dogs were given 10 mgm. per kilogram, which amounted to an actual dose of about 100 mgm., since most of the dogs weighed very close to 10 kgm. In all cases, the urine following

TABLE 5

The secretion of antiseptic urine by dogs following the intravenous administration of small doses of chlor-mercury fluorescein

DOG	DOSE	APPARENT EFFECT UPON ANIMAL	ALBUMIN	CASTS	NUMBER OF COLONIES WHICH DEVELOPED IN AGAR PLATE CONTAINING 0.1 CC. OF URINE WHICH HAD PREVIOUSLY BEEN INOCULATED AND INCUBATED FOR 24 HOURS		
					Urine obtained just before injection	Urine obtained 1 hour after injection	Urine obtained 5 hours after injection
	<i>mgm.</i>						
13	5	None	—	None	∞	0	
21	5	None	—	None	∞	∞	∞
11	5	None	—	None	∞	0	
12	5	None	—	None	∞	0	
20	5	None	—	None	∞	0	∞
10	5	None	—	None	∞	0	
18	35	None	—	None	∞	0	∞

All specimens of urine were inoculated with one loop of a twenty-four hour broth culture of colon bacillus.

Examinations for casts and albumin were made on the first or second day following the administration of the drug.

this dose was very strongly antiseptic, and the antiseptic action was maintained for at least five hours. In all cases, the drug was so concentrated in the urine that 0.1 cc. of the urine added to 10 cc. of melted agar rendered the latter antiseptic towards the colon bacillus. In other words one hundred parts of melted agar plus one part of urine (after 100 mgm. dose), plus one loop of a broth culture of the colon bacillus, plated immediately and incubated, showed no growth; the control of inoculated agar without the drug-containing urine of course showed several

thousand colonies. A similarly conducted experiment did not completely inhibit the development of the staphylococcus aureus, the plate showing about 1000 colonies. The length of time necessary for the urine (following the 100 mgm. dose) to *kill* (rather than simply to inhibit) the colon bacillus was not determined, although we know that this time is more than one hour and less than twenty-four hours. Preliminary experiments conducted by plating at intervals 0.1 cc. amounts of inoculated urine (obtained after 100 mgm. dose) led us to believe that the colon bacillus was killed in a few seconds; but, since it was later demonstrated that the plates showed growth when *loops* (instead of the larger 0.1 cc. amounts) of inoculated urine were transferred, it was proved that the apparent rapid germicidal action was in reality merely antiseptic action exerted in the agar by the small quantity of urine (0.1 cc.) transferred.

As demonstrated by the following experiment, a 5 mgm. per kilogram dose is also strongly antiseptic. With a catheter which had been used in the animal room for weeks without sterilization, a female dog (18) was catheterized before and after the administration of 5 mgm. per kilogram (actual dose 35 mgm.). Since no aseptic precautions whatever were taken, both specimens of urine were necessarily contaminated with the flora of the vagina and of the unsterile catheter. Furthermore, the specimens were collected in test tubes which were chemically, but not bacteriologically clean, and were filtered through unsterile filters. Plates poured immediately, using 0.1 cc. of urine from each specimen, showed about 10,000 colonies before injection and about 1000 colonies after injection. When the urine was incubated twenty-four hours before pouring plates, that taken before injection showed a countless number of colonies, while that taken one hour after injection was sterile (see table 5).

Man. An initial experiment proved that the drug was rapidly excreted by man as well as by animals. Up to the present we have given the drug to only three patients, in doses of 5, 10 and 25 mgm., respectively. After preliminary examination showed that the urine was normal, the experiment was conducted with exactly the same technique as was used for dogs and rabbits.

Specimens of urine obtained by aseptic catheterization just before the administration of the drug and 1 hour afterwards were inoculated and incubated, and plated twenty-four hours later. Those patients who received 10 and 25 mgm., respectively, secreted urine one hour later which became sterile after inoculation with the colon bacillus, staphylococcus aureus and staphylococcus albus; the control urines, as well as the urine from the patient receiving 5 mgm., permitted the growth of all three organisms, both before and after the injection. Although these data are insufficient to permit conclusions, these preliminary results with man are in accord with our findings in the case of rabbits and dogs, viz., that the antiseptis-producing dose is dependent upon urine volume rather than upon body weight, and that exceedingly small doses may be effective in spite of the large size of the animal. There was no appearance of albumin, casts or other ill effects in any of the patients who received the drug.

TOXICITY

Rabbits. As shown in table 4, the antiseptis-producing dose (5 mgm.) causes no albuminuria, and has no apparent effect upon the animal. This is also true of the 10 mgm. dose (approximately 5 mgm. per kilogram); furthermore, this dosage may be given daily, without apparent ill effect, for an indefinite period. Rabbits 49 and 54 were treated in this way, receiving daily small doses of 5 and 10 mgm. during a period of two months, until a total of 305 mgm. each had been reached. During this period, one rabbit had a slight transient albuminuria following the administration of 20 mgm. in a single dose. Other than this, neither rabbit had albumin or casts in the urine, either during or following the period of daily injection. After the drug was discontinued they appeared normal in every respect and the renal function, as measured by the phenolsulphonphthalein test, was the same as before the injections were begun, that is, 70 per cent in one hour. One of these rabbits (54) was sacrificed two weeks later. The gross autopsy was negative, and microscopical sections of the kidney were normal.

Although a daily repeated dose of 10 mgm. may apparently be continued ad libitum without effect, 20 mgm. (to an average-sized adult rabbit) will produce a transient albuminuria lasting about one day, while 20 mgm. per kilogram is usually fatal, the rabbit dying within several hours, death being preceded by diarrhoea. The lethal single dose (about 40 mgm. to a large rabbit) is therefore not much larger than the dose which may be repeated daily for an indefinite period without harm. Several other rabbits were given a total of more than 100 mgm. in daily doses of 5, 10 or 15 mgm. without the production of casts or albumin and with no other apparent effect. In conclusion it may be stated therefore that chlor-mercury fluorescein may be given to rabbits in 5 mgm. per kilogram daily doses ad libitum, without danger; 10 mgm. per kilogram is apt to cause a transient albuminuria and 20 mgm. per kilogram is usually fatal. The average lethal single dose is eight times the antiseptic-producing dose.

Dogs. The results obtained with dogs and rabbits were strikingly similar and a comparison of the two permits certain definite conclusions. For dogs as noted above the antiseptic-producing dose (5 mgm.) is the same as for rabbits; not the same per kilogram, but the *same actual dose*. Most of the dogs experimented with weighed approximately 10 kgm., and with these dogs the lethal single dose was approximately 200 mgm.; that is, 20 mgm. per kilogram, the same as with rabbits. All dogs but one died within several hours after receiving as much as 20 mgm. per kilogram, the injection being usually followed immediately by vomiting. The larger doses (50 mgm. per kilogram) caused vomiting, bowel movement and death within a few minutes.

Several dogs were given 10 mgm. per kilogram in a single dose without apparent effect, except that some of them vomited immediately after injection. Among these dogs, an occasional slight transient albuminuria without casts was noted, but this condition was also occasionally observed with normal uninjected dogs. Following this dose, no dog suffered an impairment of renal function, as demonstrated by the phenolsulphonphthalein test; nor did any dog show a decrease in the twenty-four hour

output of urine. Dog 13 survived a nephrectomy performed seven days after the administration of 100 mgm. Microscopic examination of this kidney showed normal renal tissue. Dog 17 showed no albumin or casts and no impairment of renal function (phenolsulphonphthalein test) immediately following the daily administration of 5 mgm. per kilogram, for four consecutive days. The absence of renal injury is further demonstrated by the fact that by the administration of 100 mgm. doses the ability of the kidney to secrete antiseptic urine following a 5 mgm. dose is not destroyed.

TABLE 6

Ratio of single lethal dose of chlor-mercury fluorescein to antiseptis-producing dose for rabbit, dog and man

	AVERAGE WEIGHT	ANTISEPTIS PRODUCING DOSE		SINGLE LETHAL DOSE		RATIO OF ANTISEPTIS- PRODUCING DOSE TO SINGLE LETHAL DOSE
		Grams	Grams per kilogram	Grams per kilogram	Grams	
	<i>kgm.</i>					
Rabbit.....	2	0.005	0.0025	0.02	0.04	1 to 8
Dog.....	10	0.005	0.0005	0.02	0.2	1 to 40
Man.....	70	0.01*	0.00014	0.02†	1.4	1 to 140

* Based upon one experiment only.

† Based upon the assumption that the lethal dose per kilogram for man is the same as that for rabbits and dogs (20 mgm.).

The maximum total dosage was given to dog 10 which, during a period of one month, received a total of 2040 mgm. in 10 mgm. per kilogram (120 mgm.) doses, given not oftener than once daily. The lack of renal injury is demonstrated best of all by this dog which, after receiving more than 2 grams of chlor-mercury fluorescein, showed no albuminuria or other evidence of renal impairment. When the dog was sacrificed, one month after the last injection (phenolsulphonphthalein output, 70 per cent; no albumin or casts), the gross autopsy was normal and microscopic sections of the kidney and liver were likewise normal.

As with rabbits therefore the lethal single dose for dogs is 20 mgm. per kilogram. One-fourth of this dose however or even

half may be given daily ad libitum without ill effect. The lethal single dose is approximately 40 times the antiseptis-producing dose.

Man. Obviously the lethal dose of any drug for man must be computed from values obtained experimentally in animals. As the experiments already described fix the lethal dose for dogs and rabbits at 20 mgm. per kilogram, we have as the lethal dose for a man of 70 kgm. *1.4 grams.*, if we make the probable assumption that the toxicity for man is the same as for the other animals. Moreover as dogs withstand *daily doses of 10 mgm. per kilogram over a long period without any evidence of injury*, it follows that a man should safely tolerate 0.7 gram daily. When it is considered that the antiseptis-producing dose for man may be as low as 10 mgm., and is certainly not more than 20 mgm., it is seen that it should be theoretically possible to administer an antiseptis-producing dose even as often as once every hour, thus certainly keeping the urine constantly antiseptic, and still remain well within a limit that has been shown to be entirely harmless to dogs.

SUMMARY

The synthetic compound chlor-mercury fluorescein is excreted by the kidney after intravenous injection as rapidly as is phenol-sulphonphthalein. Nearly all of the dye is excreted by the normal kidney a short time after injection but this excretion is accompanied by a cleavage in the organism into fluorescein and some form of mercury combination. The percentage of the fluorescein excreted is large as estimated colorimetrically but only a small part of the total injected mercury appears in the urine within twenty-four hours. The lack of toxic effects either immediate or cumulative after large and repeated doses makes it probable that the mercury may find its exit in the feces.

In either acid or alkaline urine (in vitro) chlor-mercury fluorescein will inhibit the development of the colon bacillus or the staphylococcus aureus in a dilution at least as great as 1-10,000. It is more efficient in acid than in alkaline urine.

The intravenous administration of minute doses (5 to 10 mgm.) to rabbit, dog or man will cause the secretion of antiseptic urine for a definite period of time. The size of the antiseptics producing dose is not proportional to body weight and is approximately the same for the three animals.

The antiseptics producing dose is well within the toxic limit. The single lethal dose for rabbits and dogs is approximately 20 mgm. per kilogram of body weight. Half this dose however (10 mgm. per kilogram) may be given daily to dogs without any ill effects. One dog received a total of more than 2 grams. Five milligrams per kilogram may be given daily to rabbits for an indefinite period. The computed lethal single dose for man is about 140 times the antiseptics producing dose.

No clinical value is yet claimed for this drug, but we believe that it is worthy of a clinical investigation. This has already been begun and will be reported upon in due time. The work reported has however accomplished a definite purpose from an experimental point of view: it has shown that minute doses of a drug possessing the necessary localizing tendency may cause an animal to secrete urine that is definitely antiseptic; and it has shown the possibilities offered in this field by synthetic chemistry.

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URINARY ANTISEPSIS—THE SECRETION OF ANTI-SEPTIC URINE FOLLOWING THE INTRAVENOUS ADMINISTRATION OF ACRIFLAVINE AND PRO-FLAVINE¹—PRELIMINARY REPORT

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The possibility of employing the principles of synthetic chemistry and subjecting a given molecule to certain modifications, so that certain desirable physiological properties are acquired, while the original properties are retained, has been demonstrated. In other publications (Davis, Davis and White, and Davis, White and Rosen) the synthesis and properties of chlor-mercury fluorescein, an experimentally efficient internal urinary antiseptic, have been described. This compound was logically synthesized according to certain definitely established principles, by the knowledge of which it was possible to couple an antiseptic agent with a molecule of certain definite chemical structure, known to possess the property of becoming rapidly localized in the urinary tract. It is not the purpose of this paper to discuss the need of an efficient internal urinary antiseptic, but merely to present briefly the results of preliminary experiments with acriflavine, which indicate that this drug may prove to be of value. The experiments with acriflavine differed essentially from those with chlor-mercury fluorescein in that the synthesis of the former was not the result of a logical procedure with an internal urinary antiseptic as the goal. The properties of this drug were discovered during the course of a routine examination of a large number of compounds, including many coal tar dyes studied with a view to determining their antiseptic properties in urine and chosen without regard to chemical structure.

¹ Preliminary report.

Browning, Gulbransen, Kennaway and Thornton have described certain properties of proflavine and acriflavine. These authors have shown that acriflavine (diamino-methyl-acridinium chloride) is a very powerful antiseptic, and that it differs from all the antiseptics in general use in that its strength is *increased* by the presence of serum. In the latter medium "its bactericidal potency for staphylococcus aureus is 800 times that of chloramine-T. or carbolic acid, and 20 times that of corrosive sublimate." They also state that with the ordinary antiseptics an efficient concentration is also sufficient to terminate all effective phagocytic action; while in the case of acriflavine, phagocytosis proceeds actively even in a concentration 200 times greater than is necessary to kill micro-organisms.

Considering the previously described loss of antiseptic action of so many of our own synthetic compounds when diluted with urine in a test tube, and considering the potency of the flavines in serum, as observed by the English authors, it was thought worth while to test the antiseptic efficiency of the latter compounds in a urine medium. Experiments conducted along these lines showed that the flavines are likewise efficient in urine, particularly so in alkaline urine. Experiments to determine their route of excretion then showed that these drugs, administered to animals either intravenously or per os, appeared in the urine. Furthermore, preliminary experiments indicate that the antiseptic strength of acriflavine is not lost by passage through the animal body, and that doses sufficient to render the urine antiseptic are not toxic. On account of the way it was necessary to discontinue this investigation just after it was well under way, and the data are therefore quite incomplete. The following results, however, seem of sufficient interest to record.

ANTISEPTIC STRENGTH IN URINE

The antiseptic strength of acriflavine and proflavine, in both acid and alkaline urine, against the colon bacillus and the staphylococcus aureus, was determined. In order that the reaction of the acid and alkaline urine used from day to day in these experi-

ments might be constant, certain definite degrees of hydrogen ion concentration were arbitrarily decided upon (p_H 6.0 on the acid side of the scale, and p_H 8.0 on the alkaline side), and the specimens of urine daily titrated to these end points. Details of the technique of the titration and of the bacteriological technique have been published elsewhere (Davis, White and Rosen). The table of antiseptic strength (table 1) indicates the highest dilution of the drug in urine which permitted growth during an incubation period of twenty-four hours. Each dilution (in a sterile test tube) was inoculated with one loop of a twenty-four hour broth culture of colon bacillus or staphylococcus aureus, and

TABLE 1
The antiseptic strength of acriflavine diluted in urine

	COLON BACILLUS		STAPHYLOCOCCUS AUREUS	
	Acid urine (p_H , 6.0)	Alkaline urine (p_H , 8.0)	Acid urine (p_H , 6.0)	Alkaline urine (p_H , .80)
Dilution which inhibits development.....	1: 5,000	1: 100,000	1: 75,000	1: 100,000
Dilution which permits growth.....	1: 7,500	1: 200,000*	1: 100,000*	1: 200,000*

* In repeating the experiment several times it was observed that even these extreme dilutions usually killed the organism, but occasionally permitted growth. This discrepancy was probably due to variations in the composition of the urine, other factors being constant.

at the end of twenty-four hours 0.1 cc. was plated. A sterile plate indicated an inhibitory concentration of the drug, while the presence of numerous colonies showed that growth had taken place during the incubation period.

Table 1 also shows the remarkable effect which the reaction of a urine medium may have in influencing the efficiency of an antiseptic. Acriflavine restrains the growth of both organisms in *alkaline* urine in very high dilution (1:100,000). In acid urine also it is equally efficient against the staphylococcus, but loses its effect on the colon bacillus in a dilution somewhere between 1:5,000 and 1:7,500. This result may be considered fortunate, because a urinary antiseptic, relatively more efficient in alkaline

urine, is much more desirable than one which acts better in acid urine. It is a relatively simple matter to render the urine alkaline, whereas there is no known method of causing more than a very slight increase in the acidity of urine. Using mono-sodium phosphate, Henderson and Palmer were unable to produce a change in the hydrogen ion concentration of the urine greater than from p_H 6.8 to p_H 6.0; whereas, with sodium bicarbonate they were able to easily make the urine very alkaline. The highest degree of alkalinity reached by this medication was p_H 8.7.

The technique for testing the *germicidal* strength of acriflavine in urine was the same except that the inoculated dilutions were incubated for only one hour (instead of twenty-four) before 0.1 cc. was transferred to the agar plate. Table 2 shows that acri-

TABLE 2
The germicidal strength of acriflavine diluted in urine

	COLON BACILLUS		STAPHYLOCOCCUS AUREUS	
	Acid urine (p_H , 6.0)	Alkaline urine (p_H , 8.0)	Acid urine (p_H , 6.0)	Alkaline urine (p_H , 8.8)
Dilution which kills in 1 hour.....	1: 200	1: 1,000	1: 1,000	1: 1,000
Dilution which fails to kill in 1 hour	1: 500	1: 10,000	1: 10,000	1: 10,000

flavine does not kill rapidly, and that its value lies therefore in its antiseptic rather than in its germicidal strength. Here, as with the antiseptic test, is shown a relative weakness against the colon bacillus in acid urine.

Experiments with proflavine show that this drug likewise retains its antiseptic powers in urine, and likewise exhibits a relative weakness against the colon bacillus in acid urine. It further resembles acriflavine in that it inhibits the colon bacillus in high dilution in alkaline urine, and inhibits the staphylococcus regardless of the reaction of the urine. The two drugs are quite similar, excepting that acriflavine is effective in somewhat higher dilution, and would therefore seem to be the drug of choice for use as an internal urinary antiseptic.

EXCRETION

The appearance time of acriflavine in the urine after administration has not been determined, nor have accurate quantitative estimations been made. This would be difficult since the yellow color of the drug renders a colorimetric estimation inaccurate. A 10 mgm. intravenous dose of proflavine or acraflavine (to rabbits) appears in the urine at sometime during the first hour after inject on, and continues to be excreted for about four hours. Further than this we have no accurate data.

THE SECRETION OF ANTISEPTIC URINE

Technique. Experiments determining the antiseptic properties of the urine of rabbits after the administration of acriflavine were carried on with exactly the same technique as has been published elsewhere in describing the results obtained with chlor-mercury fluorescein as an internal urinary antiseptic. The animals were catheterized, with aseptic precautions, just before, and at intervals of two and four hours after, the intravenous administration of the drug. These specimens of urine, in sterile test tubes, were inoculated from twenty-four hour broth cultures of the colon bacillus (or staphylococcus aureus or albus, as indicated in table 3), and incubated at 37°C. for twenty-four hours, after which 0.1 cc. was removed from each tube and plated. Sterile plates (indicated in table 3 by the sign, 0) showed that the organisms had died during the incubation period, and that the drug was therefore present in inhibitory concentration; while plates in which countless numbers of colonies developed (indicated in table 3 by the infinity sign, ∞) showed that the organisms had grown and developed, and that the urine therefore contained no antiseptic agent.

Results. Table 3 shows the antiseptic properties of the urine of rabbits obtained both before and after the intravenous administration of acriflavine in amounts varying from 10 to 50 mgm. As indicated, the colon bacillus and the staphylococcus aureus and albus were used for inoculating; all together in some experiments (one loop of each), and separately in other experi-

ments, the specimen of urine in the latter case being divided into three portions. As in testing the antiseptic strength of acriflavine in voided human urine, each sample of urine, after inoculation with the designated organism, was incubated at 37°C. for twenty-four hours, after which 0.1 cc. was transferred to melted

TABLE 3

The secretion of antiseptic urine by rabbits following the intravenous administration of acriflavine

RABBIT	DOSE	APPARENT EFFECT UPON ANIMAL	ORGANISM USED FOR INOCULATING URINE	NUMBER OF COLONIES WHICH DEVELOPED IN AGAR PLATE CONTAINING 0.1 CC. OF URINE WHICH HAD PREVIOUSLY BEEN INOCULATED AND INCUBATED FOR 24 HOURS			
				Urine obtained just before injection	Urine obtained 2 hours after injection	Urine obtained 4 hours after injection	Urine obtained 8 hours after injection
	<i>mgm.</i>						
65	50	Died after three days	A	1,000 %		0	
			B	∞		0	
			C	1,000 %		0	
64	25	None	A	∞	0		∞
			B	∞	0		0
			C	∞	0		
62	10	None	A	∞		0	
			B	∞		0	
			C	∞		0	
60	10	None	A	∞	0		
			C	∞	0		
65	10	None	A	∞		0	
60	10		A, B, C	∞	0		∞
63	10		A, B, C	∞	1,000 %		
76	10	None	A, B, C	∞	0		
69	10	None	A, B, C	∞	0		

Tubes of urine were inoculated with 1 loop of a twenty-four-hour broth culture of the designated organism.

A = *Colon bacillus*; B = *Staphylococcus aureus*; C = *Staphylococcus albus*; 0 = no colonies; ∞ = an infinite number of colonies; 1000 % = approximately 1000 colonies.

agar and plated. As designated by the infinity sign (∞), the plates from those specimens of urine obtained before the administration of the drug showed great numbers of colonies; while the plates poured from the specimens of urine obtained at intervals of two and four hours afterward were sterile with but one excep-

tion. This rabbit had received only 10 mgm. of the drug and the urine was inoculated with all three organisms. Furthermore, the plate contained only several thousand colonies and therefore showed that growth had been restricted. Of three specimens of urine obtained after an eight-hour interval, two allowed the colon bacillus to grow, while one (after a 25 mgm. dose) still inhibited the staphylococcus aureus. The urine of one rabbit (not listed in table 3) obtained after the injection of 10 mgm. of *proflavine*, likewise showed an antiseptic action.

Following the administration of acriflavine to rabbits in 10 mgm. amounts *by mouth*, although the drug appeared in the urine, no antiseptic properties could be demonstrated. The effect of larger doses by mouth is as yet undetermined.

Preliminary experiments with dogs, in attempting to produce antiseptic urine by the intravenous administration of acriflavine were unsuccessful. This finding is in accord with the results shown in table 1, comparing the relative antiseptic strength of acriflavine in inhibiting the development of the colon bacillus in acid and alkaline urine. According to this table the drug is many times more efficient in alkaline urine. Since rabbit urine is normally alkaline, and dog urine acid, this would seem to be the logical explanation of the success of the drug in the former medium, and its failure in the latter. A preliminary experiment, attempting to improve the efficiency of acriflavine in dog urine by rendering the latter medium alkaline, was successful, but we have not sufficient data on this subject to permit conclusions.

TOXICITY

As to toxicity, preliminary experiments prove that the dose sufficient to produce antiseptic urine in rabbits is well within the toxic limit. None of the rabbits showed any effect from a 10 or 25 mgm. dose. A 50 mgm. dose, however, although without apparent effect when given by mouth, caused death during the following two or three days if given intravenously. Autopsies revealed no typical lesions. No effect upon any of the dogs was observed following the administration of comparatively large

amounts, one dog receiving a 200 mgm. dose without ill-effect (about 20 mgm. per kilo) and several others were given as much as 100 mgm. The English authors state that proflavine, 1:50, produces slight irritation of the conjunctiva; acriflavine does so at 1:150. By subcutaneous injection in mice, they were able to demonstrate that the flavines "are comparatively little toxic for the body as a whole."

CONCLUSIONS

Acriflavine and proflavine retain their antiseptic action when diluted in urine, and in this respect differ from many standard antiseptics.

Although strongly antiseptic in both acid and alkaline urine, these drugs display a relative weakness in inhibiting the colon bacillus in acid urine. They are efficient in very high dilution, however, against the colon bacillus in alkaline urine, and against the staphylococcus in urine of any reaction.

When administered by mouth or intravenously to rabbits and dogs, acriflavine and proflavine appear in the urine in less than one hour, and continue to be excreted for about four hours. Quantitative determinations of percentage of excretion have not been made.

Following the intravenous administration of 10 mgm. doses of acriflavine to rabbits the urine is rendered antiseptic between the second and the fourth hours. The exact time limits have not been determined. Corresponding doses by mouth did not produce antiseptic urine. Following the same dose per kilogram to dogs, no antiseptic action in the urine could be demonstrated. This may be due to the acidity of dog urine, as compared with the alkalinity of rabbit urine.

Rabbits tolerate 25 mgm. doses of acriflavine without apparent effect, but do not survive 50 mgm. (intravenous) doses. No apparent effect upon 10 kgm. dogs was observed following intravenous doses of 100 mgm. and 200 mgm.

Preliminary experiments indicate that acriflavine and proflavine may prove to be of value for internal use in *alkaline* in-

fections of the urinary tract. The synthetic compound chlor-mercury fluorescein, the experimental fitness of which as an internal urinary antiseptic has been described elsewhere, is relatively more efficient in *acid* urine.

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URINARY ANTISEPSIS—THE ANTISEPTIC PROPERTIES OF NORMAL DOG URINE

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A previously described series of experiments, conducted with the synthesis of an internal urinary antiseptic as the ultimate goal, involved an investigation of the antiseptic properties of the urine of dogs and rabbits, both before and after the intravenous administration of various drugs, which had previously been shown to be antiseptic in vitro. As a control on all such experiments, a specimen of the animal's urine, obtained just before the administration of the drug, was inoculated and incubated under exactly the same conditions as the specimen obtained after medication, in order that the two might be contrasted, and thus conclusively prove that any antiseptic action exhibited by the urine was due to the drug. This technique led to the surprising observation that normal, drug-free, dog urine may be of itself antiseptic; that is, that those specimens of urine, obtained before the dog had been subjected to any medication whatever, occasionally prevented the growth of the colon bacillus. This antiseptic action, however, was not constant, that is, it was not exhibited by all dogs, nor by the same dogs on all occasions. On account of the serious obstacle therefore encountered in accurately controlling experiments dealing with urinary antiseptics, an investigation of the nature of the antiseptic action of normal dog urine was undertaken, and an attempt made to determine the underlying factor responsible for the intermittent or sporadic nature of this antiseptic action. The experiments were confined largely to dogs, although sufficient work was done with rabbits to establish the fact that rabbit urine possesses the same property with the same irregularity.

These findings are in keeping with the inconstancy of the results reported by Rovsing and Melchior and others, and more recently by Eisendrath and Schultz (1), and by David (2), in their attempts to produce experimental cystitis in dogs by injecting organisms into the non-traumatized, unobstructed bladder. The latter author includes an extensive bibliography and a very interesting résumé of the experimental work carried on by various authors in attempting to determine the route of ascending renal infections. For a detailed statement of the problem on urinary antisepsis mentioned above, and a description of the drugs (more than 200 synthetic compounds were investigated), and of the technique of administration, see publication by Davis (3), Davis and White (4), and Davis, White and Rosen (5).

TECHNIQUE

The method, in brief, was simply to inoculate and incubate specimens of urine obtained by catheterization, and determined whether or not the urine acted as a favorable culture medium. All catheterizations were done with aseptic precautions. For dogs, a small, stiff, gum, olive-tipped catheter, sterilized by boiling, was used, after washing the penis and irrigating the external urinary meatus with 1-10,000 bichloride. Specimens of urine obtained by this procedure were almost invariably free from gross contamination, as demonstrated by agar plates inoculated from each. These plates, poured immediately after catheterization, and containing 0.1 cc. of urine, were almost always sterile, but occasionally showed several scattered colonies. Rabbits were catheterized by the same method, with a small, soft, rubber catheter.

For inoculating, a strain of colon bacillus (twenty-four hour culture), isolated from a case of pyelitis in man, was used. In some experiments, however, other organisms also were used, including staphylococcus aureus, staphylococcus albus, typhoid and paratyphoid. The staphylococcus aureus was isolated from the renal pelvis (human), and the staphylococcus albus from the bladder of a dog accidentally found to have a chronic, persistent

bacteriuria. Each specimen of urine was divided into two or more equal portions (dependent upon the number of varieties of organisms to be used) in sterile test tubes, and these portions (all but one) were inoculated with one loop of a twenty-four-hour broth culture of the desired organism. One portion was incubated without inoculation in order to determine the sterility of the specimen. If this uninoculated tube was found to be sterile after incubation, then it could be assumed that growth present in any of the inoculated tubes was due to the inoculating organism and not to contamination. Immediately after inoculation, in order to prove beyond possible doubt that the inoculation had been successful, and that each specimen of urine contained organisms, 0.1 cc. of urine was transferred from each tube (with a sterile capillary pipette) to melted agar and plated. These plates, very roughly estimated, usually contained several thousand colonies (designated in the tables as 1000*).

All tubes of urine were then incubated for twenty-four hours at 37°, after which 0.1 cc. was again transferred from each tube to a tube of melted agar and plated. All plates were inspected at the end of twenty-four hours and again after forty-eight hours. A comparison of the series of plates poured immediately after inoculation of the urine, with those poured after twenty-four hours' incubation, readily determined whether or not growth had taken place. Those plates showing countless numbers of colonies (designated in the tables by the infinity sign, ∞) proved that that particular specimen of urine had acted as a favorable culture medium; while the plates which were sterile, or which contained only a very few colonies, indicated an antiseptic urine. It was very surprising to observe that a tube of urine, proved by the before-incubation plate to contain several thousand organisms per 0.1 cc., could become sterile during incubation; while in other specimens of urine the organisms grew and developed, so that each plate contained millions of colonies.

With each experiment was run a control of human urine, subjected to exactly the same conditions as the dog urine and on all occasions the organisms grew and developed in human urine. It would seem therefore that human urine differs essentially from dog urine in this respect.

TABLE 1

The antiseptic properties of the urine obtained by the first catheterization of twenty-four dogs, chosen at random

DATE	DOG	HYDROGEN ION CONCENTRATION	NUMBER OF COLONIES WHICH DEVELOPED IN AGAR PLATE CONTAINING 0.1 CC. OF URINE	
			Transferred immediately after inoculation	Transferred after 24 incubation for twenty-four hours
July 2.....	2 D	5.8	1000 %	0
	3 D	6.8	1000 %	0
July 5.....	4 D	5.8	1000 %	∞
	5 D	6.2	1000 %	0
	6 D	7.0	1000 %	∞
August 25.....	7 D	5.5	1000 %	0
	8 D	5.8	1000 %	0
	9 D	6.0	1000 %	0
December 2.....	11 H	6.0	1000 %	0
	12 H	5.0	1000 %	0
	13 H	5.8	1000 %	0
December 7.....	4 H	5.8	1000 %	0
	5 H	6.4	1000 %	∞
	6 H	6.2	1000 %	∞
March 30.....	7 H	5.6	1000 %	0
	8 H	5.6	1000 %	0
	9 H	6.8	1000 %	0
	1 B	5.8	1000 %	0
	2 B	6.0	1000 %	∞
	3 B	6.0	1000 %	0
May 10.....	3 C	6.2	1000 %	0
	4 C	6.4	1000 %	0
	7 C	5.8	1000 %	0
	9 C	5.6	1000 %	∞

Each tube of urine was inoculated with 1 loop of a broth culture of the colon bacillus. 0 = no colonies; 100 % = several thousand colonies.; ∞ = infinite number of colonies.

OCCURRENCE OF ANTISEPTIC URINE

Different dogs. Each of the dogs used was catheterized many times and the antiseptic properties of the urine determined on as many different occasions. Table 1 includes, however, only the result of the initial catheterization of each one of these dog, and illustrates therefore the frequency of the occurrence of antiseptic urine among dogs chosen at random. It will be seen that out of twenty-four dogs, the urine from eighteen, obtained by catheterization, inoculated with one loop of a twenty-four-hour

TABLE 2

The daily variation in the antiseptic properties of the urine of the same dogs

DATE	NUMBER OF COLONIES WHICH DEVELOPED IN AGAR PLATE CONTAINING 0.1 CC. OF INOCULATED INCUBATED URINE					
	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
December 6.....	0	0	0	∞	∞	0
December 7.....	0	0	0	0	∞	0
December 8.....	0	0	0	∞	∞	100
December 9.....	0	0	0	0	0	∞
December 10.....	0	0	0	0	0	200
December 11.....	∞	0	∞	0	0	0
December 12.....	0	0	0	∞	∞	0
December 13.....	∞	0	0	∞	0	∞
December 14.....	∞	0	0	0	0	∞
December 15.....	0	0	∞	0	∞	∞

Each tube of urine was inoculated with one loop of a twenty-four hour broth culture of the colon bacillus. 0 = No colonies; ∞ = an infinite number of colonies.

broth culture of the colon bacillus and incubated for twenty-four hours, not only failed to act as a favorable culture medium for these organisms, but killed them in less than twenty-four hours. The urine, however, from the remaining six dogs, obtained, inoculated and incubated under exactly the same condition, permitted a profuse growth of the same organism. All of the dogs were on the same diet (meat only) and all of them had access to an unlimited amount of water.

Same dogs on different days. In order to determine the constancy of the antiseptic property of the urine of any given

dog, catheterizations were performed daily on six dogs for a period of ten days, and each specimen of urine inoculated and incubated, always under the same conditions and with the same strain of colon bacillus. Table 2 shows the intermittent character of the antiseptic action, and the daily variation in the composition of the urine of each individual dog, as regards its suitability as a culture medium. It will be seen that on no day during the ten was the colon bacillus killed by the specimens from all six dogs; nor was there a day when all six permitted growth. Usually one or two specimens out of the six, rarely three, acted as favorable culture media. The urine of each individual dog permitted growth on an average of three times and killed the bacillus the remaining seven. Dog 2 was particularly interesting in that during this experiment the urine did not once fail to kill; furthermore, during a total of thirty catheterizations of this dog, on thirty consecutive days, the colon bacillus grew in only one specimen of urine.

THE EFFECT ON VARIOUS ORGANISMS

In view of the possibility that this antiseptic action might be specific against the colon bacillus, the following experiments were undertaken to determine the fitness of dog urine as a culture medium for organisms other than the colon bacillus. As shown in table 3, specimens of urine from three dogs, and one human control, were each divided into eight (2 cc.) samples in sterile test tubes. Of each series of eight tubes, seven were inoculated with various organisms, including bacillus coli communior (two strains), bacillus coli communis (two strains), typhoid bacillus, paratyphoid and staphylococcus, while the remaining one was incubated without inoculation, in order to determine the sterility of each series of eight, and thus rule out the question of contamination. Plates poured according to the usual technique (after twenty-four hours' incubation, transferring 0.1 cc. from each tube) demonstrated that the urine from all three dogs uniformly killed all the organisms excepting the staphylococcus aureus. The latter organism grew profusely in each case. The

control series of human urine permitted a growth of each of the organisms. It would seem therefore that the antiseptic action of dog urine is directed against organisms of the colon-typhoid group, and has no effect on the staphylococci.

Further experiments were therefore carried out comparing the effect of dog urine on the colon bacillus, staphylococcus aureus and staphylococcus albus. On different occasions a total of twenty-seven specimens of urine were used, from eleven different dogs. Each specimen was divided into three samples, inoculated with colon, aureus, and albus respectively, and incubated for

TABLE 3
The effect of dog urine upon various organisms

ORGANISM	NUMBER OF COLONIES WHICH DEVELOPED IN AGAR PLATE CONTAINING 0.1 CC. OF INOCULATED INCUBATED URINE			
	Dog 11 p _H 6.0	Dog 12 p _H 6.0	Dog 13 p _H 5.8	Human urine p _H 6.0
Colon (strain a).....	0	0	0	∞
Colon (strain b).....	0	0	0	∞
Colon (strain c).....	0	0	0	∞
Colon (strain d).....	0	0	0	∞
Typhoid.....	0	0	0	∞
Paratyphoid.....	0	0	0	∞
Staphylococcus aureus.....	∞	∞	∞	∞
Not inoculated.....	0	0	0	0

Each tube of urine was inoculated with one loop of a twenty-four-hour broth culture of the designated organism. 0 = No colonies; ∞ = an infinite number of colonies.

twenty-four hours, after which 0.1 cc. from each sample was plated. The results are shown in table 4. Out of a total of twenty-seven specimens, the staphylococcus aureus was killed only eleven times. The colon bacillus was killed twenty times (in all but seven), showing the same occasional or sporadic growth as described above. The staphylococcus albus, however, grew invariably. From a consideration of this table we may conclude that the colon bacillus is usually killed by normal dog urine, while the staphylococcus aureus usually grows in the same medium. The particular strain of staphylococci albus used (isolated from

dog urine) always grows in normal dog urine. Staphylococci are therefore more resistant than organisms of the colon-typhoid group.

TABLE 4

The effect of dog urine upon the colon bacillus, staphylococcus aureus and staphylococcus albus

Dog.....	NUMBER OF COLONIES WHICH DEVELOPED IN AGAR PLATE CONTAINING 0.1 CC. OF INOCULATED, INCUBATED URINE																			
	30	31	31	31	31	31	31	32	32	33	33	33	34	34	34	34	34	35	36	37
April.....	1	1	3	6	7	10	12	1	3	6	10	12	1	3	6	7	10	12	10	10
Colon bacillus.....	0	0	0	0	∞	0	∞	0	0	∞	0	0	0	0	0	∞	∞	0	∞	∞
Staphylococcus aureus..	0	∞	0	∞	∞	∞	∞	0	∞	∞	∞	0	0	0	0	∞	∞	∞	0	∞
Staphylococcus albus....	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞	∞

Each tube of urine was inoculated with one loop of a twenty-four hour broth culture of the designated organism. 0 = No colonies; ∞ = an infinite number of colonies.

RATE OF DEATH OF COLON BACILLUS

The above experiments determine only whether or not there are living organisms present in the specimens of urine at the end of twenty-four hours. To determine the length of time necessary to kill these organisms, equal (0.1 cc.) amounts were taken from tubes of inoculated (colon bacillus) dog urine at regular (one-hour) intervals and plated. Table 5 gives the number of colonies which developed in the plates after forty-eight hours. All three speci-

TABLE 5

The length of time necessary to kill the colon bacillus in normal dog urine

DOG	REACTION	NUMBER OF COLONIES IN PLATES Poured AT VARYING INTERVALS AFTER INOCULATION WITH ONE LOOP OF A BROTH CULTURE OF COLON BACILLUS. EACH PLATE CONTAINS 0.1 CC. OF URINE								
		Minutes	Hours							
		10	4	5	6	7	8	10	11	12
11	p _H 6.0	1000 %	66	70	40	39	33	5	0	0
12	p _H 6.0	1000 %	5	2	0	0	0	0	0	0
13	p _H 5.8	1000 %	37	25	12	7	15	20	2	0

Tubes of urine were incubated at 37°C. during intervals between transfers.

mens of dog urine showed a very rapid germicidal action during the first four hours, the number of colonies dropping from several thousand to less than one hundred. The urine of one dog showed only two colonies in the five-hour plate, and was sterile after six hours. The plates from the other two specimens of urine showed a more gradual decrease in the number of colonies and did not become sterile until the twelfth hour.

EFFECT OF HYDROGEN ION CONCENTRATION

In seeking for an explanation of intermittent antiseptic power, one naturally thinks first of variation in urinary reaction. This explanation would seem to be all the more plausible in view of the findings of Shohl and Janney (6), who have shown that the colon bacillus fails to grow in human urine at certain definite acid (p_H 4.8 and alkaline (p_H 9.2) end points. After determining and recording the hydrogen ion concentration of more than one hundred specimens of urine, before testing the antiseptic strength of these specimens, we were able to demonstrate no relationship whatever between the reaction of dog urine and its suitability as a culture medium. The results in this large series of hydrogen ion determinations all lay between p_H 5.6 and 7.0. In different specimens it was frequently observed that the organisms both grew and failed to grow at both extremes of this range, and at all intermediate points. Furthermore, this range of variation in the reaction of dog urine (p_H 5.6 to 7.0) lies well within the range determined by Shohl and Janney (p_H 4.8 to 9.2) as limiting the growth of the colon bacillus in human urine, the reaction of which has been artificially adjusted after voiding. A comparison of tables of daily hydrogen ion determinations (not listed in this paper) with the tables showing the results of antiseptic tests (tables 1 and 2), furnishes further proof of the lack of relationship between urinary reaction and urinary antiseptis. A few striking examples comparing the two are listed in tables 6 and 7. Table 6 compares the urines of different dogs tested on the same date and therefore subjected to the same conditions. It will be seen that on December 6 the organisms grew in the

urine of dog 4, which had a hydrogen ion concentration of 6.8; while the urines of dogs 1 and 3, one of which was more acid and the other more alkaline, both killed the organisms. Likewise, on December 11 the urine of dog 4 killed, while the urines of dogs 1 and 3, one of which was more acid and the other more alkaline, both permitted growth. Table 7 compares the reaction and antiseptic property of specimens of urine obtained from the same dogs on different days. The urine of dog 1, on December

TABLE 6

Showing the lack of relationship between the hydrogen ion concentration and the antiseptic power of normal dog urine (different dogs on same days)

	DECEMBER 6			DECEMBER 11		
	Dog 1	Dog 4	Dog 3	Dog 3	Dog 4	Dog 1
Hydrogen ion concentration.....	6.6	6.8	7.0	5.8	6.2	6.4
Number of colonies.....	0	∞	0	∞	0	∞

Each tube of urine was inoculated with one loop of a twenty-four-hour broth culture of the colon bacillus. 0 = No colonies; ∞ = an infinite number of colonies.

TABLE 7

Showing the lack of relationship between the hydrogen ion concentration and the antiseptic power of normal dog urine (same dogs on different days)

	DOG 1			DOG 3		
	Decem- ber 14	Decem- ber 8	Decem- ber 13	Decem- ber 7	Decem- ber 11	Decem- ber 6
Hydrogen ion concentration.....	5.8	6.2	6.4	5.6	5.8	7.0
Number of colonies.....	∞	0	∞	0	∞	0

Each tube of urine was inoculated with one loop of a twenty-four-hour broth culture of the colon bacillus. 0 = No colonies; ∞ = an infinite number of colonies.

8, showed a hydrogen ion concentration of 6.2, and on this day killed the colon bacillus; yet permitted growth on December 13 and 14, although on one of these days it was more acid and on the other more alkaline. The specimens of urine from dog 3 showed a similar lack of relationship between reaction and antiseptis. It may therefore be concluded that the hydrogen ion concentration is not the essential factor in determining the antiseptic properties of dog urine.

DISCUSSION

On the theory that the antiseptic action might be due to some removable substance, soluble in the ordinary extractives, samples of dog urine were extracted with benzene, ether, chloroform, carbon bisulphide, carbon tetrachloride, and acetic ether, and the extracted urine submitted to the routine antiseptic tests. No results were obtained by this method, the samples of extracted urine behaving just as the unextracted controls. As to the possible effect of the specific gravity of the urine in influencing its antiseptic property, although we had begun an investigation of this point, it was necessary to discontinue the experimental work before there were sufficient data available upon this subject to base an opinion. A likewise incomplete series of experiments, comparing the suitability for culture media of specimens of dog urine before and after passage through a Berkefeld filter, demonstrated a distinct tendency for the organisms to fail to grow in the filtered, inoculated portions, even though there might be profuse growth in the unfiltered inoculated controls. No similar effect was observed following the filtration of human urine. Complete data, establishing the fact that dog urine (previously suitable) may be rendered unsuitable as a culture medium by filtration, would tend to show that the so-called antiseptic properties of dog urine might better be explained as due to lack of nutritive substances. At the time when the war abruptly terminated this experimental work, no definite conclusions had been arrived at as to the cause of the failure of organisms to grow in dog urine.

SUMMARY

Normal dog urine, obtained by aseptic catheterization, shows a distinct antiseptic action, which is particularly marked against organisms of the colon-typhoid group, less effective against the staphylococcus aureus, and entirely inert against at least one strain of staphylococcus albus.

This antiseptic action is not constant for all dogs, nor for the same dogs on all occasions. It was exhibited, however, by the urine of one dog in twenty-nine out of thirty catheterizations.

Dog urine, inoculated with the colon bacillus and incubated, may become sterile during as short a period as six hours.

The antiseptic action of dog urine bears no relationship to the hydrogen ion concentration, nor is it influenced by the action of various extractives on the urine.

Of those specimens of dog urine which act as suitable culture media, some may be rendered unsuitable by passage through a Berkefeld filter.

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THE SURGICAL TREATMENT OF GONORRHEAL EPIDIDYMITIS

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The treatment of epididymitis, which is a frequent and painful complication of gonorrhea, has for many years been the source of much discomfort and unpleasantness to both the physician and the patient. It is not the mild type of this condition to which I wish to call the reader's attention, but rather to the severe type, beginning with pyrexia and severe pain, confining the patient to his bed, and enlisting all the ingenuity and skill which the physician has at his command to combat it.

Baerman has shown that, in the vast majority of cases, there is definite abscess formation usually accompanied by an inflammatory hydrocele. Even in those cases in which he removed from 4 to 5 cm. of pus by aspiration he was unable clinically to demonstrate any degree of fluctuation, as the pus was generally contained in the innermost part of a hard infiltrated nodule. In cases which showed only moderate sized nodules located in either the head or the tail of the epididymis, he was able to aspirate one or two drops of serous fluid, from which a pure culture of gonococcus was grown.

Judging from the foregoing consideration of the pathology of this condition, it would seem that the therapeutic measures usually employed are distinctly unsurgical. It seems incredible, for in no other cases of inflammatory effusions or localized collections of pus do they permit nature to take its course. It is, therefore, difficult to understand the conservatism prevalent in cases as acute as gonorrheal epididymitis. Indeed it contradicts all modern surgical principles.

Surely the old objection that the patient will not tolerate surgical interference is not applicable, as there is no class of

patients so eager to subject themselves to even the most drastic measures, as those afflicted with gonorrheal epididymitis. Another argument frequently advanced against radical treatment is that strapping the testicle and providing the patient with a well fitting suspensory often permits the patient to go about his duties with comparative ease. This, however, holds good in only a few cases, the majority being treated with rest in bed and opiates to relieve pain. It is this latter class which presents a field for more radical treatment.

The method which we have used has for many years been embodied in text-books, but to be employed only when pus was distinctly evident, and the scrotal wall was adherent to the testicle. Hagner in 1902 recommended the operative treatment for epididymitis, but for reasons unknown it has never been generally adopted by the profession. The operation which we wish to recommend, though not as complicated as that of Hagner's, seems to adapt itself admirably to the purpose. It consists simply in making an incision about $\frac{1}{2}$ inch in length through the scrotal wall and tunica vaginalis, immediately over the most swollen area of the epididymis, and permitting the serous or purulent exudate to escape. If the fluid which escapes is serous in character, as is prevalent in the vast majority of cases, the incision is closed with one silk-worm gut suture one or two strands of catgut being left for drainage. The latter is generally removed after twenty-four hours. If pus is present the incision is packed with a small strip of plain gauze and the wound allowed to granulate. Either a local anesthetic or gas was used. Immediate relief is obtained from this simple procedure, and the patient is able to resume his duties in a few days and shortly thereafter to submit to treatment for his urethritis.

The following cases which were operated upon by the writer may be of interest in demonstrating the results of the above treatment.

CASE NUMBER	DURATION	EPIDIDYMITIS	STAY IN HOSPITAL	RESUMED DUTIES	SERUM	PUS
	<i>days</i>		<i>days</i>	<i>days</i>		
1	4		2	5	+	+
2	3		4	5	+	
3	8		6	10		
4	1		3	4	+	
5	5		2	3	+	
6	4		1	2	+	
7	6		3	6		
8	2		2	4	+	
9	6		2	3	+	
10	3		1	3	+	
11	5		4	7	+	
12	2		1	2	+	
13	8		3	4	+	
14	3		1	2	+	

Average stay in hospital 2.5 days.

Average number of days patient was able to resume duties 4.26 days.

CALCULUS IMPACTED IN A VESICAL DIVERTICULUM REMOVED BY HIGH FREQUENCY CAUTERIZATION

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Since the introduction of intravesical high frequency spark cauterization by Edwin Beer in 1910, designed primarily to destroy bladder excrescences, this procedure has found many adherents among urological surgeons in the treatment of various pathological conditions occurring in the urethra and in the bladder. The uses now made of high frequency spark cauterization in urology are almost legion. Among the conditions in which this method has been employed successfully might be mentioned: the treatment of bladder ulcers; to enlarge a ureteral ostium containing an impacted calculus; the cauterization and subsequent reduction of median lobe prostatic enlargements; the destruction of growths within the posterior urethra; and, the sterilization of infected glands of Littre within the anterior urethra.

The writer herewith submits another use to which intravesical high frequency cauterization can be applied. The relative infrequency with which cases of calculus impacted within a vesical diverticulum are encountered and the simple means by which many such stones can be removed prompts the report of the case.

Mr. A. G., farmer, seventy-nine years of age, was referred to the writer in April, 1918, with the following history:

Ten years previously he had been operated upon for a urethral stricture and an hypertrophy of the prostate; suprapubic prostatectomy and external urethrotomy performed at that time. Since then he had remained in fair health up until one year ago when he noticed that urinary frequency developed—both diurnal and nocturnal—that ardor urinae accompanied every effort at voiding, marked urgency increasing as time went on and pain

over bladder region rather severe of late. All these symptoms were markedly accentuated when he came under the writer's care. For years his family physician has been passing a 24 Charrière urethral sound into the bladder once a month in order to assist patient to void more freely. Urinary stream fair at examination. Patient had never had any attacks of fever with this trouble and had never noted hematuria. The general physical examination revealed nothing of importance bearing on the present condition.

Urinalysis showed: a trace of albumin, no sugar, few hyaline and granular casts, few red blood cells, much pus and many colon bacilli. Phenolsulphonephthalein test, two-hour reading, gave 46 per cent. Blood-urea 0.5 gram per liter.

Under local (apothesine 2 per cent) anesthesia cystoscopy was performed at Hotel Dieu. Due to a contracture of the vesical neck, the cystoscope was introduced with some difficulty. The bladder was distended with warm sterile water (bladder capacity 350 cc.) and it was noted that the entire vesical mucosa was more deeply injected than normal, most marked however on the trigone. Ureteral ostia were normal as to size, shape and function. Upon the right lateral wall of the bladder, above and behind the right ureteral ostium was seen a small, white mass adherent to the vesical wall and about the size of a pea. At first it was thought to be a small papilloma—for to the eye it appeared as a miniature cauliflower-like growth. There was something about it which also suggested a calculus. That it might be a vesical growth encrusted with urinary salts was considered a possibility. To determine its character a no. 6 silk ureteral catheter was introduced through the cystoscope into the bladder and pushed up against the mass. The tumor seemed solid. A Bugbee high frequency cautery electrode, also sized no. 6 Charrière, was then introduced and an Oudin spark current applied to the mass. No effect whatever was produced. It was then considered that the mass must be a calculus and as it was fixed to the side of the bladder wall, immovable, it must be a calculus impacted within a vesical diverticulum. Figure 1 illustrates the condition actually existent. The high frequency

spark was then applied to the bladder wall surrounding the impacted stone (i.e., the neck of the diverticulum). The electrode tip was deliberately pushed into the mucosa. Multiple areas were so treated and by using a wide spark gap marked penetration was obtained. These cauterizations caused the patient no pain whatever and the calculus was completely encircled with charred spots in about ten minutes. The cystoscope was then removed and patient returned to bed.

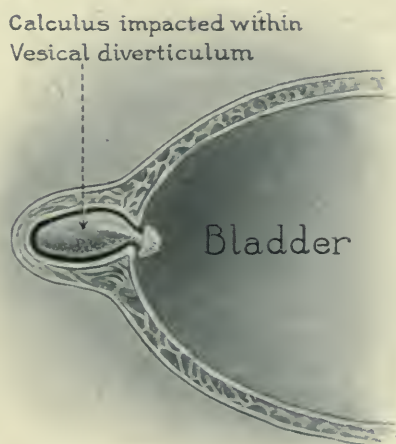


FIG. 1.

Two days later, a second cystoscopy was performed under local anesthesia. An operating cystoscope was used at this sitting as further intravesical operative measures were contemplated. Upon inspecting the right lateral bladder wall where the calculus had been first seen, the examiner noted a small excavated hole (the diverticulum) already beginning to collapse, with sloughing edges. Upon examining trigone, a dumb-bell shaped stone was seen lying free in the bladder. Calculus was grasped with a pair of Buerger forceps and easily removed. The stone weighed 320 mgm. and measured 16 mm. long and 7 mm. thick.

Both ureters were then catheterized to kidneys and the separate urines collected. Urinalysis showed a trace of albumin and a few hyaline and granular casts from each kidney but no pus or bacteria.

Not the least interesting feature of the case was the curious shape of the calculus and the fact that the greater part of the stone was concealed within the vesical diverticulum. This demonstrates most forcibly that no estimate of the size of bladder diverticulum stones can be made by cystoscopy alone. An x-ray picture will undoubtedly be of aid at times. In this instance the calculus was expelled before a radiographic study had been contemplated.

CLASSIFICATION OF THE DISTURBANCES OF SPHINCTERIC CONTROL RESULTING FROM WOUNDS AND CONTUSIONS OF THE LUMBO-SACRAL REGION (WITH AND WITHOUT EXTERNAL WOUND)¹

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TRANSLATED FROM THE FRENCH BY HUGH HAMPTON YOUNG

In the present war the enormous explosive force of large shells and bombs causes contusions, both internal and external, even at a considerable distance. Moreover, the concussion caused by large masses of earth, stone and similar substances produces a special type of injuries without external wound which at the beginning of the war were often classified as slightly injured or even as malingerers, although in reality they may have extensive internal injuries the pathogenesis of which I shall sketch below.

This report is confined to lumbo-renal concussions and contusions, all of them caused by missiles of war with or without external wound, with or without disturbance of sphincteric control. The classification is based on 65 cases observed in the Service Centrale d'Urologie d'Orleans.

Disturbances of sphincteric control (retention or incontinence) due to war wounds are quite frequent. Their correct clinical interpretation is difficult because of the great variety of symptoms which obscures the similarity of cause. Nevertheless these two phenomena, so clinically dissimilar, i.e., incontinence and retention, are physiologically speaking in the same class and clinically they appear successively or alternately in a given individual. They usually result from lumbar or sacral concussion and from wounds of the pelvis or of the adjacent regions; although

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incontinence may be primary and retention secondary, the opposite (primary retention and secondary incontinence) is the usual condition. Occasionally the appearance of disturbance of sphincteric control is delayed. The anal sphincter is sometimes involved but less often and less gravely than that of the bladder. Disturbance of the sexual function may show itself in the form of priapism but oftener as impotence. Concussion or contusion of the cerebro-spinal tract causes symptoms that are essentially transitory, amenable to treatment and to permanent cure as contrasted with the symptoms resulting from actual wounds of the central nervous system. But disturbance of sphincteric control is likely to be more persistent than other symptoms even when it is due to concussion. It is indeed one of the dominant signs of this condition.

This report, based on 65 observations, covers the frequency, the variety and the persistence of derangements of micturition, whether retention or incontinence, primary or secondary, transitory or permanent. The symptomatology, as I have seen it and as it has recently been studied by Claude and Porak, is confused and disconcerting. Because of the irregular distribution of the lesions there is a "sciatic type" upon which it is usually wise not to operate.

For the present we confine our attention to the neurological aspects of the condition. It is extremely difficult if not impossible always to classify the symptoms anatomically according to the segments of the spinal cord involved. The following segments are recognized:

1. Cerebral segments: The incontinence or retention is due to nervous or psychic disturbance, whether emotional, sub-conscious or mechanical.
2. Medullary segment: The spinal centers at the level of the twelfth dorsal are those involved in lumbar concussions.
3. Root segment: With the well-known classical syndrome of lesion of the cauda equina.
4. Sympathetic and ganglion segment: which can only be diagnosed by exclusion.
5. Plexus segment: Involved in pelvic wounds.

6. Peripheral segment: Involved in perineal and para-vesical wounds.

In order to distinguish accurately the segment or segments, the injury of which has occasioned incontinence or retention of urine, it is necessary to follow a definite diagnostic plan. The following new classification is suggested:

A. *Lumbo-renal and sacral concussion* with or without hematuria, with or without disturbance of sphincteric control, but *without external wound*:

1. Lumbar concussion *without sphincteric disturbance* characterized by *pain in the spine*.

2. Lumbar concussion *with sphincteric disturbance* and with or without other motor disturbances.

3. Lumbo-renal concussion with *hematuria* and with or without sphincteric disturbance: (a) Without lumbar contusion; (b) with lumbar contusion (rare).

4. Sacral and pelvic concussion with *vesical or urethral bleeding* and with or without sphincteric disturbance (concussion of the bladder).

B. *Sphincteric disturbance with lumbo-sacral or pelvic wound* and with or without temporary or prolonged paraplegia:

1. Sphincteric disturbance due to lumbo-sacral wound but *without prolonged paraplegia*.

2. Sphincteric disturbance with lumbo-sacral wound and prolonged or permanent *paraplegia*.

3. Sphincteric disturbance with wound or foreign body proximate to the lumbo-sacral region.

4. Associated disturbance of the sphincters of *rectum and bladder* after pelvic wounds.

5. Sphincteric disturbance due to *cerebral* trauma.

There exists a true syndrome due to lumbar concussion characterized by three symptoms—lumbar pain, hematuria and sphincteric disturbance.

As to *prognosis* all that we can say is that the hematuria and paralysis usually disappear rapidly while the lumbar pain and the sphincteric disturbance may be more persistent. The lumbar pain type (A-1) is the mildest form resulting from a

concussion of the lumbar region whether directly due to the projectile or because the patient has been thrown down and injured his loin. I take no account of those mild and temporary cases when the patient can reach the ambulance unaided but only of grave conditions that prohibit all movement, comparable to severe lumbago, and in which the severity of the injury is attested by subsequent ecchymosis or hematoma.

We may note in passing that these patients are not urological cases in the true sense of the word. They come to our wards because they have pain "in the kidneys" and also because they sometimes pass blood, but except for this complication they should rather be sent to centres of neurology or of mechanotherapy which treat them better than we can do.

I shall, therefore, take no account of motor or sensory troubles seen in 30 of my cases, bed sores (3 cases) or vaso-motor disturbances (scarcely any). Apart from these troubles we may classify our 65 cases as follows:

	<i>Cases</i>
Sphincteric disturbance with lumbo-sacral wound and without prolonged paraplegia.....	17
Lumbo-renal concussion with hematuria, without external wound, with or without sphincteric disturbance.....	16
Lumbar concussion with sphincteric disturbance, without external wound, with or without motor disturbance.....	10
Sphincteric disturbance with wound or foreign body adjacent to the lumbo-sacral region.....	8
Sphincteric disturbance with lumbo-sacral wound with prolonged or permanent paraplegia.....	5
Sacral or pelvic concussion with vesical or urethral bleeding, with or without sphincteric disturbance.....	4
Lumbar concussion without sphincteric disturbance (lumbar pain type).....	3
Sphincteric disturbance of rectum and bladder following pelvic wound.....	1
Sphincteric disturbance due to cerebral trauma.....	1

Finally in 33 of these cases there was no external wound; in 32 there were wounds of greater or less severity. Two of these died of their wounds.

PATHOGENESIS AND PATHOLOGICAL ANATOMY

The chief interest in this type of cases centers about the sphincteric disturbances of the bladder neck and anus and especially in the injuries to the deeper parts occurring in cases that show no external wound. Our colleagues Guillain and Heitz were among the first to note these cases and the latter has collected 5 cases of organic paraplegia resulting from shell explosion without external wound.

The sphincteric function is controlled by the fourth and fifth sacral segments and the uro-genital centers are situated at the level of the conus which lies on the level of the twelfth dorsal vertebra. In this region the following four centers are superposed: (1) Ano-spinal center of Masius; (2) vesico-spinal center of Bunge; (3) genito-spinal center of Gianuzzi; (4) erection center of Eckhardt.

Manifestly, therefore, any lesions of this region may determine corresponding peripheral functional disturbance, and lesions of the same region of the spinal cord may result in incontinence, retention, priapism or impotence, for these phenomena although so different are controlled by these adjacent centers, whether the injury is to the center itself or to the cauda equina producing the syndrome so well studied by Lhermit.

Apart from such physiological localizations, what are the anatomo-pathological lesions that cause these sphincteric disturbances? The lack of autopsy material leaves this question still in the domain of hypothesis, but we may well believe that the lesions vary according to the clinical type. In the painful type they are doubtless purely parietal, such as rupture of muscular fibers in the sacro-lumbar muscle produced by the phenomenon spoken of as a "snap of a whip," in other cases rupture of ligaments or bone with or without hematoma, with or without infiltration of blood or lymph.

In the hematuric type there is evidently an injury to the renal parenchyma, but not to the pelvis,, resulting from concussion of this organ against the transverse-costal ligament or by direct violence (16 cases).

In the graver forms with sphincteric disturbance and with or without paraplegia there are:

1. Cloudiness of the cerebro-spinal fluid, probably due to slight lesions, which disappears rapidly. That the lesion is mechanical and not inflammatory is attested by the instantaneous appearance of the hematomyelia.

2. Medullary lesions in the conus, or lesions of the blood vessels of spinal nerve roots. The following have been found: (a) Cellular changes; (b) small cortical or central hemorrhages; (c) cellular lacerations (elongation); (d) disturbance of the lymphatic peri-cellular circulation.

The preservation of sensibility to touch and heat by certain paraplegics shows that there is a lesion of the posterior nerve roots. Temporary phenomena suggest rupture of blood vessels and prompt absorption of the hematoma.

Functional disturbances with open wounds are more readily explained and vary in the quality and degree of traumatism, whether partial or transverse, the gravest form being total section of the spinal cord resulting from severe fractures or dislocations of the vertebrae.

DISSOCIATION OF VESICAL AND ANAL SPHINCTERIC DISTURBANCES

One of the most curious characteristics of these injuries is the lack of association noted by disturbance of the vesical sphincter and that of the anal sphincter. Thus, among my 65 cases 5 at most had fecal retention and 3 fecal incontinence (chiefly in the form of diarrhoea) making a total of 8 cases of anal sphincteric disturbance. This fact is most curious in view of the close proximity of the spinal centers presiding over the action of these two sphincters, there being only a few millimetres between them. It is thus difficult to explain a disturbance of one (whatever the cause) while the other remains intact.

PROGNOSIS AND TREATMENT

The prognosis is often grave and the treatment often inefficient.

1. For lumbar pain the patient is placed in bed and hot moist compresses applied at first followed later by cauterization.

2. For the hematuria L  chelle water is almost specific, given in doses of 2 cc. every hour, with absolute rest and small doses of hexamethylenamin to prevent renal infection.

3. When there is sphincteric disturbance:

a. For false incontinence due to relaxation of the internal sphincter the treatment is epidural injection.

b. If the incontinence is due to retention the retention catheter is employed.

c. If the retention is complete without incontinence the catheter will be passed at regular intervals and instillations of silver nitrate employed in strength of 1:1000. We have cured several cases by this treatment.

4. If the sphincteric disturbance is accompanied by paraplegia the prognosis is very grave for the paraplegia may prove permanent. However, the following signs we have found suggestive of temporary paraplegia due to transitory organic change, i.e.,

a. Fibrillary contractions in the muscles when the patient tries to lift his two legs.

b. Normal reflexes of the lower extremities.

c. Preservation of good general condition and absence of bed sores.

d. Slight improvement in the first few days.

Nevertheless, I repeat the prognosis in these cases is extremely grave both as to the paralysis of the lower extremities and as to that of the sphincters.

The lesions of the spinal cord and of the lower spinal nerves, particularly those of the cauda equina, are thus extremely varied in their pathology and consequently in their clinical manifestations. Hence, it is that the classical syndrome of lesion to the cauda equina characterized by motor and sensory disturbance of the lower extremities, sphincteric disturbance and vaso-motor and trophic disturbance, is rarely found.

We have noted various associations of these multiple symptoms with sphincteric disturbance but scarcely ever with trophic disturbances. Bed sores and vaso-motor changes are very rare.

This is frequently due to the topography of the lesions and the multiplicity of the nerves whose functions are well known and

individual. Hence the clinical dissociation—the absence of classical syndrome.

The mechanical cause of injury in our cases was as follows:

Open wounds

	<i>Cases</i>
a. Due to shell fragment.....	25
b. Due to bullets:	
(1) Shrapnel.....	7
(2) Rifle.....	4
(3) Machine gun.....	2

The sphincteric disturbance may be classified as follows:

Concussion or contusion

	<i>Cases</i>
a. Due to falling.....	12
b. Due to burial.....	6
c. Due to fall after being thrown into the air.....	7
d. Due to air concussion.....	2
Primary incontinence.....	7
Primary retention.....	34
Late or secondary incontinence.....	17
Late or secondary retention.....	3

It is important to note that in the great majority of cases the retention is primary and that 10 of the cases of incontinence occurred late following retention. In the actual state of our knowledge it is indeed difficult to give a plausible explanation for this succession of events.

THE STRUCTURE OF THE VERUMONTANUM—A STUDY OF THE ORIGIN AND DEVELOPMENT OF ITS INHERENT GLANDULAR ELEMENTS

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The last decade has brought forth a wealth of clinical study and observation on the possible rôle of pathological conditions of the verumontanum underlying certain disorders of the posterior urethra. It has now been well established that symptomatic relief is afforded in many instances by therapeutic measures applied directly to the verumontanum. A satisfactory explanation of this *modus operandi* is not always apparent nor will this be entirely understood until we have a clearer conception of the structure, physiology and pathology of this organ.

First described by Morgagni (1) and later discussed by Albinus (2) and by Schlichting (3), the verumontanum remained an object of only passing interest until Weber (4) pointed out the striking developmental analogy between the sinus pocularis contained therein and the uterus of the female. Later studies concerning the physiology of the verumontanum by Walker (5) and clinical observations by Swinbourne (6), Ruggles (7), Randall (8), Rytina (9) and others have done much to increase our knowledge of this little understood but highly important structure. More recently Rytina (10) has given us a comprehensive study of its histology and gross anatomy as seen in adult life.

Concerning the development of the verumontanum there is a surprising dearth of any accurate information. The notation that the region of the urogenital sinus wherein empty the two primary excretory ducts (ejaculatory ducts) becomes raised into a definite prominence (Müller's hillock) and that this later contains the sinus pocularis or prostatic utricle and the terminal

portions of the two ejaculatory ducts comprises about all of our knowledge regarding the formation of the verumontanum. In a more detailed report (11) the study of the origin and development of the verumontanum has been recorded at length.

At the thirteenth week of fetal life the region of the urethral floor wherein open the two primary excretory ducts (common ejaculatory ducts) is raised in the form of a small oval prominence which is the enlarged hillock of Müller or Müller's tubercle now termed the verumontanum. This prominence measures 0.7 mm. long, 0.7 mm. wide, and 0.4 mm. in height. Its upper portion has its origin in three longitudinal striae starting just below the internal sphincter which increase in size as they traverse the posterior urethra and finally become a part of the verumontanum itself. Below at its inferior margin three similar striae emerge and gradually decrease in size until they become a part of the urethral floor. The verumontanum at this time is composed of a mass of undifferentiated mesenchymatous cells budding forth from the floor of the prostatic urethra not unlike those going to form the prostatic intertubular substance and the walls of the urethra. It is covered by a triple cell layer of epithelial cells which is continuous with the lining epithelium of the posterior urethra. The terminal portions of the ejaculatory ducts course through the verumontanum and open on either side of its summit or tip. The prostatic utricle at this stage is contained partly within the verumontanum and partly within the prostatic substance and exists as an elongated sac-like cavity 0.4 mm. in length. At this time there is no evidence of any tubular elements entering into the formation of the verumontanum. Its mesenchymatous cells, however, are more closely packed and take the stain more deeply than those entering into the formation of the intertubular prostatic substance.

By the fourteenth week the verumontanum has increased notably in height and now measures 0.7 mm. long, 0.7 mm. wide, and 1.3 mm. in height. Only one stria of elevation is observed entering into its formation above and a single midline elevation proceeds from the terminal portion below. The substance of the organ is still composed of a mass of undifferentiated mesenchy-

matous cells but about the two ejaculatory ducts and the prostatic utricle they are more closely packed and take the stain with greater avidity than in the earlier specimen. The mucous covering of the verumontanum in the meantime has undergone very definite changes. Over the upper portion near the termination of the superior stria and continuing well up to include the

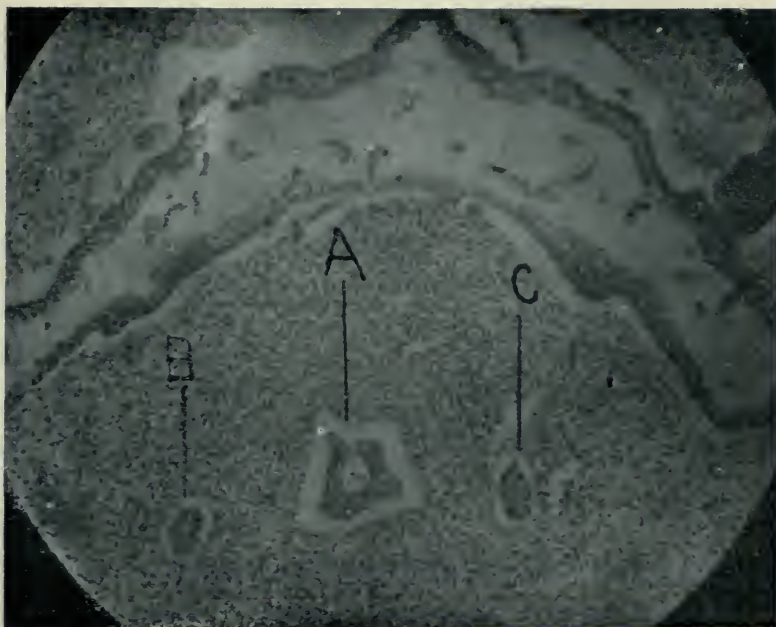


FIG. 1. SPECIMEN 768C, CARNEGIE EMBRYOLOGICAL COLLECTION

Fetus 80.3 mm. long, thirteen weeks old. Transverse section through the upper portion of the verumontanum. A, prostatic utricle; B, left ejaculatory duct; C, right ejaculatory duct.

tip or summit of the organ, the epithelial covering has become extremely irregular forming many pit-like depressions. These in certain areas have become well marked invaginations which dip boldly into the substance of the verumontanum forming definite glandular tubules. These first observed glandular elements of the organ are of unmistakable mucous membrane

origin and occupy a position over the upper portion and in the peripheral zone being situated for the most part above the openings of the ejaculatory ducts. The utricle at this time is contained entirely within the verumontanum and exists as a sword shaped closed cavity 0.6 mm. in length lined with several layers

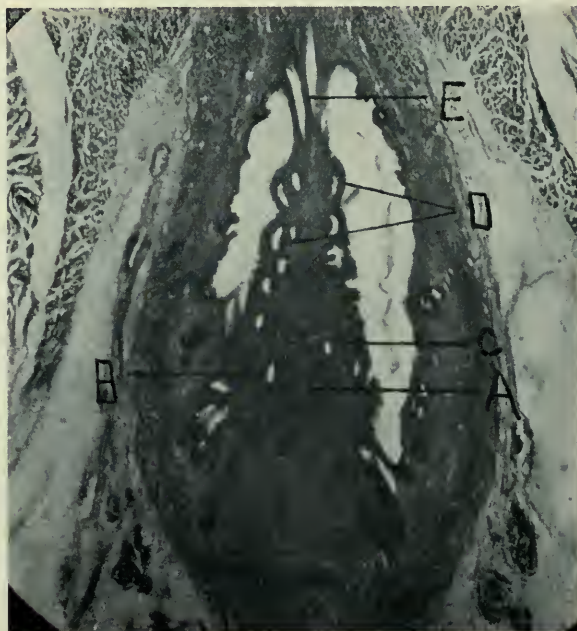


FIG. 2. SPECIMEN 1358E, CARNEGIE EMBRYOLOGICAL COLLECTION

Fetus 105 mm. long, fourteen weeks old. Transverse section through the upper portion of the verumontanum. A, prostatic utricle; B, left ejaculatory duct; C, right ejaculatory duct; D, peripheral gland tubules of mucous membrane origin; E, fibrous strands connecting the tip of the verumontanum to the roof of the urethra (an anomaly).

of epithelial cells. On either side of the utricle the ejaculatory ducts run in a parallel path to open on either side of the tip of the verumontanum into the posterior urethra.

The next specimen studied at sixteen weeks disclosed several interesting facts. At this period the verumontanum measures

1.25 mm. long, 0.6 mm. wide and 0.4 mm. high. The three superior striae previously mentioned are readily identified and merge without incident to form the upper portion. Below three similar folds proceed from its terminal portion and gradually decrease in size until they become lost in the urethral floor in

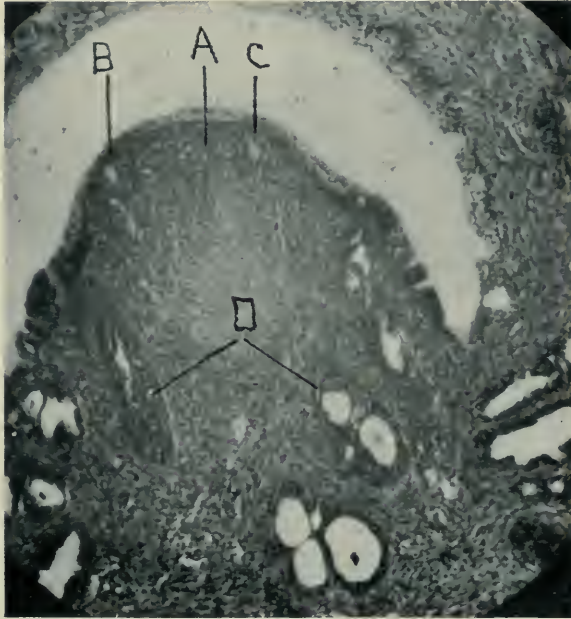


FIG. 3. SPECIMEN 1018, CARNEGIE EMBRYOLOGICAL COLLECTION

Fetus 130 mm. long, sixteen weeks old. Transverse section through the middle of the verumontanum. *A*, prostatic utricle; *B*, left ejaculatory duct; *C*, right ejaculatory duct; *D*, gland tubules of prostatic origin (middle lobe) entering into the base and sub-peripheral portion of the verumontanum.

the direction of the membranous urethra. The substance of the verumontanum is still made up for the most part of undifferentiated mesenchymatous cells. The epithelial covering is relatively free from irregularities over the upper portion of the verumontanum in this specimen but below the openings of the ejaculatory ducts the characteristic pit formation is well observed.

Still further down toward its inferior margin and in the peripheral zone definite tubules of mucous membrane origin are present lying well imbedded within the mesenchyme of the verumontanum.

Just below the mucous membrane of the upper half of the organ the previously undifferentiated mesenchyme has become more specialized, a portion of which can now be recognized as forming a stroma-like sheath. Enclosed within this sheath or capsule-like covering are located the prostatic utricle and ejaculatory ducts. In addition are certain gland tubules situated in the subperipheral zone. By careful study through many serial sections these are found to originate from the prostatic middle lobe (suburethral portion) and to have been pushed upward from their original site by the slanting course of the ejaculatory ducts and utricle to occupy a position within the verumontanum itself. This group of tubules constitutes the second set of glandular elements contained within the verumontanum which by their origin and position are clearly apart from those of mucous membrane origin observed first in the specimen at fourteen weeks. All of the tubules thus far observed, namely, those of mucous membrane origin occupying the peripheral zone and those of prostatic origin located in the subperipheral area open through the lateral aspects of the verumontanum into the prostatic urethra. The utricle measures 0.6 mm. in length in this specimen and exists as a closed cavity lined with several layers of epithelial cells. Its contour in general is sword shaped. The ejaculatory ducts after an upward slanting parallel course open without incident on either side of the verumontanum near its tip.

In the specimen at nineteen weeks only two striae enter into the formation of the verumontanum above, the middle elevation being lacking. Below toward the membranous urethra only one stria is present, namely, the central elevation, the two lateral ridges here being absent. The differentiation of the peripheral mesenchyme into a stroma sheath is even more strikingly shown at this time and within this sheath a few undifferentiated cells still persist. The epithelium covering the verumontanum shows

the usual irregularity and pitting with definite invaginations and tubule formation though this is here not so strikingly shown as in the previous stages. In the subperipheral zone are found the tubules of prostatic origin (from the suburethral portion of the middle lobe) as was first observed during the sixteenth week. For the most part all the tubules extend parallel to the

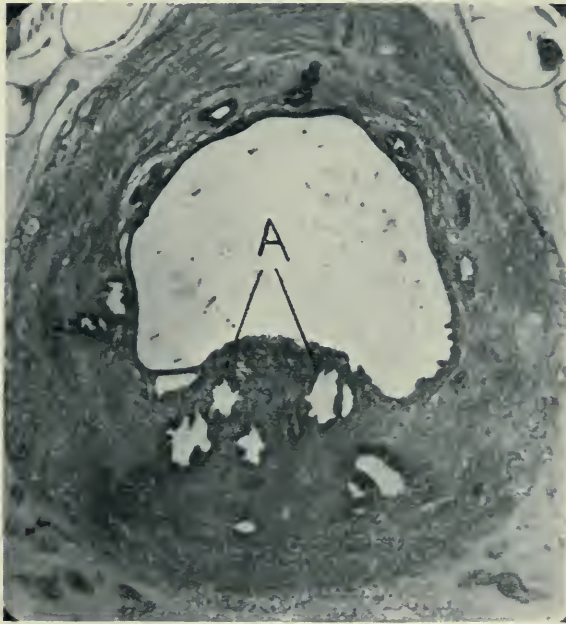


FIG. 4. SPECIMEN 1040, CARNEGIE EMBRYOLOGICAL COLLECTION

Fetus 171.4 mm. long, nineteen weeks old. Transverse section through the lower portion of the verumontanum. A, gland tubules of prostatic origin (middle lobe).

long axis of the verumontanum with their blind ends pointing upward toward the internal sphincter and their openings toward the membranous urethra. The specimen studied at nineteen weeks shows no striking changes over the previous one for the interval just passed has been a period of growth of the structures already present rather than the formation of new tubules. Dur-

ing this time the tubules of prostatic origin have definitely increased in number and all open along the sides of the verumontanum into the posterior urethra. The utricle at this time is contained partly within the prostatic substance and partly within the verumontanum proper and still exists as a sword shaped closed cavity 1.2 mm. in length. The ejaculatory ducts open into the posterior urethra on either side of the verumontanum and show no evidence of any cell accumulation at their orifices that might be construed to be the anlage of a sphincter ejaculatorius as has been suggested by some writers. The verumontanum measures at this time 2.5 mm. long, 0.9 mm. wide, and 0.5 mm. in height.

At the twenty-first week of fetal life the three superior striae are easily recognized and soon become lost in the irregularities of the epithelial covering of the upper third of the verumontanum. Below the three inferior striae gradually decrease in size until they reach the level of the urethral floor. The verumontanum measures at this time 1.4 mm. long, 1.0 mm. wide, and 0.7 mm. in height. As in the earlier specimens its epithelial covering is quite irregular forming many pits or depressions and in places well defined tubules. These tubules occupy a position in the peripheral zone of the organ and all open directly into the posterior urethra along its sides or lateral aspects. In addition to being located entirely along its periphery they are found more particularly in its upper third toward the internal sphincter.

The second group of tubules of prostatic origin are here well formed and occupy a position in the subperipheral zone situated for the most part along the middle third of the organ. These tubules some five or six in number likewise all open into the urethra along the lateral margins of the verumontanum. The utricle is first encountered in the substance of the prostate before the real elevation of the verumontanum is reached but for the greater part is enclosed within the prominence of the verumontanum. It still remains as a closed cavity lined with several layers of epithelial cells and measures 1.4 mm. in length. The ejaculatory ducts pursue an upward slanting course and open on either side near the tip of the verumontanum. As in the

previous specimens its lower or inferior third, i.e., that portion from which arise the inferior striae, is made up entirely of stroma cells.

At the twenty-fifth week the usual three superior striae entering into the formation of the verumontanum above and the



FIG. 5. SPECIMEN 1171, CARNEGIE EMBRYOLOGICAL COLLECTION

Fetus 178 mm. long, twenty-one weeks old. Transverse section through the upper portion of the verumontanum. *A*, Prostatic utricle; *B*, left ejaculatory duct; *C*, right ejaculatory duct; *D*, tubules of mucous membrane origin; *E*, pitting of the mucous membrane to form tubules.

three similar elevations proceeding from it below are easily recognized. The peripheral portion of the upper third is now composed almost entirely of glandular tubules of mucous membrane origin all of which open into the urethra along its sides. Beneath the periphery the layer of deeper tubules of prostatic origin is encountered. A few of these are seen occupying a posi-

tion in the upper third of the organ but for the most part they are confined to the middle third of the structure.

In addition to the two sets of tubules mentioned above there is noted at this time a series of evaginations from the cavity of the utricle itself. These take the form of a definite pitting of the



FIG. 6. SPECIMEN 1172, CARNEGIE EMBRYOLOGICAL COLLECTION

Fetus 221 mm. long, twenty-five weeks old. *A*, Prostatic utricle showing the irregularity of its lining membrane; *B*, left ejaculatory duct showing the irregularity of its walls; *C*, right ejaculatory duct; *D*, gland tubules of mucous membrane origin.

mucous lining and in places of unquestioned tubule formation situated for the most part in the midline and extending dorsalward toward the base of the verumontanum. The utricle exists entirely within the verumontanum as a closed cavity 0.5 mm. long. At this time is noted an elongation of the roof of the utricle cavity toward the urethra indicating the path of its fu-

ture opening at the summit or tip of the verumontanum. The ejaculatory ducts show in this specimen a slight irregularity of their walls but this is not of a degree sufficient to be called pit formation and is not as extensive as observed in the cavity of the utricle. The ducts open on either side of the verumontanum into the posterior urethra.

The next specimen studied at thirty-one weeks shows the customary three superior striae merging to form the verumontanum above and four similar ridges of elevation proceeding from its substance toward the urethral floor below. It measures at this time 4.25 mm. long, 1.4 mm. wide, and 0.3 mm. in height. As has been previously pointed out the epithelium covering the upper third of the organ is extremely irregular, giving rise to the characteristic pitting and tubule formation, which glandular elements are confined entirely to the peripheral zone. Below in the portion termed the subperipheral strata, the tubules of prostatic origin are readily recognized. All of the above mentioned glandular elements open directly into the posterior urethra through the sides of the verumontanum itself. The third group of tubules occupying a position in the center of the organ as periutricular structures are easily identified by their origin from the evaginating utricle lining. This latter group without exception empty entirely into the cavity of the utricle. Between the twenty-fifth and thirty-first weeks the utricle opens into the prostatic urethra and at the latter time it has a wide bifurcated lumen somewhat suggestive perhaps of its origin from the fusion of the two Müllerian ducts. It measures at this time 3.5 mm. in length. The ejaculatory ducts show some irregularity of their walls during their course through the verumontanum but otherwise they appear as in the earlier stages and open on either side of the tip of the verumontanum. The orifices of the ejaculatory ducts are gaping and there is no evidence of any sphincteric fibers at their termination.

The last specimen studied, at birth, shows the three usual superior striae entering into the formation of the verumontanum above and the same number proceeding from its inferior portion below toward the membranous urethra. Over the upper third

of the organ the irregularity of the mucous covering is still present and beneath in the peripheral zone the tubules of mucous membrane origin are readily recognized. As further sections are studied toward the middle of the organ the second group of tubules of prostatic origin appear. Both of these two sets of tubules are contained within the stroma sheath of the veru-

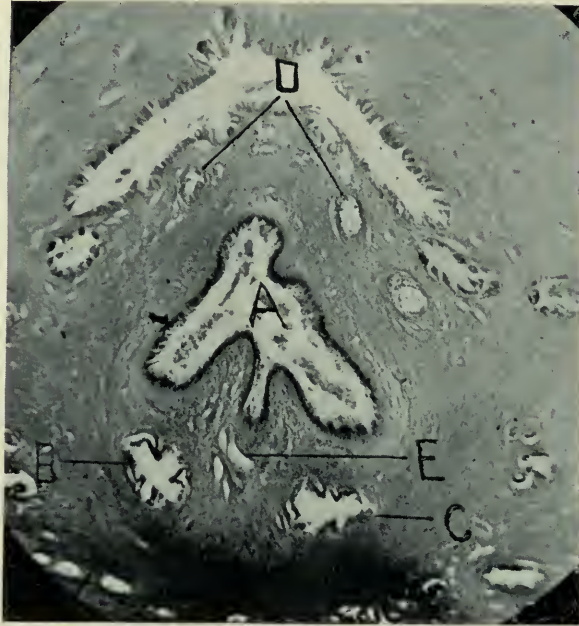


FIG. 7. SPECIMEN 7, JOHNS HOPKINS HOSPITAL OBSTETRICAL SERVICE

Fetus 276 mm. long, thirty-one weeks old. Transverse section through the upper portion of the verumontanum. *A*, Prostatic utricle; *B*, left ejaculatory duct; *C*, right ejaculatory duct; *D*, gland tubules of mucous membrane origin; *E*, gland tubules of utricular origin later opening into the prostatic utricle.

montanum which was formed from the outlying strata of mesenchyme. The tubules of prostatic origin, all situated in the sub-peripheral zone, comprise over half of the glandular elements of the middle third of the organ and are most numerous just beyond the openings of the utricle and ejaculatory ducts. The extreme inferior portion of the verumontanum is made up only of stroma

covered with the characteristic epithelial cells continuous with the lining of the urethra.

The utricle exists as a sac-like cavity lined with several layers of epithelial cells and opens through a wide gaping orifice into the posterior urethra at the tip of the verumontanum. The



FIG. 8. SPECIMEN 8, JOHNS HOPKINS HOSPITAL PATHOLOGICAL SERVICE

Fetus 338 mm. long at birth. Transverse section through the tip of the verumontanum. *A*, Opening of the prostatic utricle into the urethra; *B*, opening of left ejaculatory duct; *C*, right ejaculatory duct; *D*, tubules of mucous membrane origin; *E*, gland tubules of prostatic origin; *F*, gland tubules of utricular origin.

third group of tubules arising from the evagination of the lining of the utricle are now quite numerous and occupy a position in the central zone of the verumontanum. These are definitely separated from the other two groups of glandular elements and open directly into the cavity of the utricle. They are situated for the most part in the midline directly beneath the floor of

the utricule though a few scattered nests of tubules are found along the lateral margins of the cavity. The utricule measures at this time 0.3 mm. in length and is cone shaped with its apex at the opening into the urethra. The ejaculatory ducts in their course through the verumontanum retain to a considerable measure the irregularity of their walls observed in the last specimen but in no case do they give rise to any tubule formation. They finally open simultaneously on either side of the verumontanum near its tip with orifices widely dilated and with no evidence of any sphincteric fibers present.

SUMMARY

1. At the thirteenth week of fetal life the verumontanum exists as a cell mass budding forth from the mid-portion of the floor of the prostatic urethra. It is composed of undifferentiated mesenchyme with no glandular elements and contains the prostatic utricule and the distal portions of the ejaculatory ducts. Three ridges, the superior striae, merge to form its elevation above and a like number, the inferior striae, proceed from its terminal portion below.

2. The first group of gland tubules, of mucous membrane origin, appear by the fourteenth week. These occupy the peripheral zone of the upper third of the organ.

3. The second group of tubular elements arising from the prostatic middle lobe (suburethral portion) appear by the sixteenth week. These for the most part are located in the middle third of the verumontanum in the subperipheral zone.

4. The third set of tubules, arising from the evagination of the lining of the utricule appear by the twenty-fifth week. These are situated in the central zone of the organ as periutricular structures.

5. The utricule opens into the urethra between the twenty-fifth and thirty-first week.

6. At birth the three sets of tubules can be readily identified located in their respective zones of distribution. Those of mucous membrane origin and those of prostatic origin open

into the urethra along the sides of the verumontanum, while those of utricular origin open directly into the cavity of the utricle.

My thanks are due Dr. Hugh H. Young, director of the James Buchanan Brady Urological Institute, and Dr. George L. Streeter of the Embryological Department of the Carnegie Foundation for their many courtesies and Dr. Charles W. Bethune of the Sister's Hospital, Buffalo, for the excellent photomicrographs.

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A STUDY OF EXPERIMENTAL GONOCOCCAL INFECTION IN ANIMALS

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The recognition of a microorganism as the probable cause of specific human disease leads in the natural course of events to attempts to cultivate the organism and to reproduce the disease by the inoculation of the germ into animals. When the organism is cultivatable and capable of producing specific disease in susceptible animals a careful study of the question of immunity and pathogenesis may be made and valuable information concerning both the specific and non-specific therapeutics of the infection may be obtained. Our present understanding of such important diseases as syphilis and tuberculosis is due to a considerable degree to this method of investigation and many other equally striking examples might be cited in connection with other infectious diseases.

Gonorrhoea has been recognized for centuries, there being indeed biblical descriptions made with sufficient accuracy to warrant present day recognition of this disease. Notwithstanding innumerable clinical reports appearing in early medical publications with reference to gonorrhoea, the beginning of modern conceptions of this infection dates back to the recognition of the causative organism by Neisser (1) in 1870. At once there were numerous attempts made to cultivate and to produce experimental infection by animal inoculation. Neisser (2) failing to get the organisms to grow on artificial media inoculated the conjunctivae of dogs with infectious pus but with entirely negative results. Sternberg (3) inoculated the eyes and urethrae of dogs and gave subcutaneous injections of gonorrheal pus to rabbits also without results. He reported inability to produce infec-

tion by intraurethral inoculation of cultures in volunteer male students. The use of plain broth as a culture medium, no doubt, explains why the infection was not reproduced.

It remained for Bumm (4) in 1885 to demonstrate that for the isolation and artificial cultivation of the gonococcus blood serum must be present in the medium. Since this time practically all attempts at animal infection were made with suspensions of artificially cultivated gonococci. By this method it has been repeatedly shown that intraurethral inoculations of pure cultures in man almost invariably cause typical infections.

Loeffler and Leistikow (5) were unsuccessful in producing infection in rabbits by inoculating the abraded conjunctivae with pure cultures of gonococci. Similarly Finger, Gohn and Schlagenhauer (6) failed to infect the urethrae or rectums of dogs or the peritoneum of white mice; but they produced an acute inflammatory condition within the knee joint of a dog by injecting pure cultures from serum agar; however they failed to recover the injected microorganisms from the lesions produced. This was also the experience of Nicolaysen (7).

In 1896 Heller (8) reported the production of gonorrheal ophthalmia in young rabbits but his work was not confirmed by Nicolaysen (7) and de Christmas (9). Wertheim (10) first treated gonococci by growing them on mouse serum agar before injecting them intraperitoneally into mice and reports a true peritonitis from the exudate of which the organisms were isolated in pure culture on the fifth day; but his results have not been confirmed by other investigators. Two-thirds of Nicolaysen's (7) white mice died within twenty-four hours after being injected intraperitoneally with gonococcus suspensions. The peritoneum showed only a clear exudate containing a few round cells and a variable number of gonococci seen in smears. The organisms could usually be cultivated from this exudate, occasionally from the heart's blood but never from the spleen. He is of the opinion that the organisms had not multiplied within the experimental animals hence death was not caused by infection proper but probably to the action of toxins liberated by autolysis. This he apparently demonstrated by producing similar results on the introduction of either dead or living bacteria.

The presence of organisms in the blood stream after intraperitoneal injection has also been shown by Wildbolz (11), Jundell (12), Morax (13) and Scholtz (14). The latter author claims that only by giving very heavy doses will there be a real increase with the appearance of organisms in the blood and other organs. This increase he believes appears during the agonal stage or even after death, while the organisms in the blood are rendered passive by the leucocytes. Pleuritis of a serofibrinous character was produced by Pizzini (15) which caused the death of the animals in three days at which time the gonococci could not be demonstrated. Subcutaneous injections were made in animals by Steinschneider and Schaeffer (16) without result while Maslofsky (17) by similar methods produced sterile abscesses. Pompeani (18) inoculated animals intravenously, recovering the organisms from the blood in forty-eight hours. Endocardial, pericardial and meningeal inoculations have been made by F. Meyer (19) and Jundell (13) with negative results. Hewes (20) claims to have produced genital gonorrhea in female dogs and Colombini (21) claims the production of similar infections in dogs and rabbits; however it has been impossible to confirm this work or that of Sorrentino (22) who reports the production of a genuine arthritis in dogs and rabbits.

An attempt was made by de Christmas (9) to produce local gonococcal infection by first paralyzing leucocytosis and causing local edema by injection of lactic acid, iodine or guaiacol before bacterial injection but he was unsuccessful, the failure in his opinion being due to the normally high temperature of rabbits and guinea-pigs. Heat fast organisms have been used under similar conditions without success (23). de Christmas was successful in obtaining positive blood cultures in rabbits forty-eight hours after an intravenous injection of gonococci, but after three days the blood was sterile. Scholtz (14) caused the death of mice in thirty-six hours by injecting the culture medium containing gonococci intraperitoneally and although the spleen and peritoneum were hyperemic and swollen, the peritoneal exudate was sterile after twenty hours. He was unable to enhance the virulence of the gonococci by inoculating the peritoneum of one ani-

mal directly from the peritoneal exudate of another. A similar lack of increased virulence was noted by de Christmas after successive passages through the blood stream of animals.

Wildbolz (11) believes that the cultures are not only toxic but may be infectious, since he injected a thirty-five-day old culture into the peritoneal cavity of a guinea-pig which caused death in thirty-six hours. There were 8 cc. of fluid in the abdominal cavity which contained many leucocytes, many of which were filled with typical gonococci. Reinoculations gave a pure culture. Since the microscopic examination of the old culture showed only a few whole organisms and the remainder partially disintegrated he feels justified in concluding that the typical gonococcal clusters were the result of multiplication within the animal body. This finding occurred but once and has not been confirmed by others. Moskalew (24) believes that gonococci are pathogenic for white mice and rabbits since after intraperitoneal injection there is at first an increase in the number of organisms followed by death of the animals. This temporary increase in microorganisms however has been shown to be due to the presence of culture medium injected with the bacteria. The sudden fall of body temperature of the injected animal may also improve the possibilities of such an increase, this sudden fall of temperature being due to shock induced by the protein injection.

Anthropoid apes seem equally as resistant to gonococcal infection as other experimental animals since Bruck (25) was unable to produce any evidence of infection in them. Torrey has demonstrated gonococci in the heart's blood of guinea-pigs five minutes after an intraperitoneal injection. The blood of these animals remained positive for twenty-four hours and gonococci could be isolated from the peritoneal exudate up to the twenty-eighth hour after such injection. He believes that animal passage increases the virulence of gonococci, since by ten animal passages the minimal fatal dose was one-fourth the original minimal fatal dose. This he reasons is due to the adaptive mechanism of the gonococcus which renders it more resistant to the lytic agencies of the host.

From a search of the literature on this subject one is forced to conclude that gonococcal infection in animals, in the sense that the organisms increase within the animals and invade their tissues, does not occur. The slight early increase in the number of organisms is explained apparently by the development on the artificial culture medium injected with the organisms, together with the lowered body temperature immediately following such an inoculation. The many positive reports are due to lesions produced by the injection of gonococcal toxin and not the result of gonococcal infection. The variability of reported results undoubtedly is due to the difference in virulence and toxin production of the various strains of gonococci as well as to the varied susceptibility of different animals of the same or different species and to the great change in the immunity of a single animal during the different seasons of the year.

With the exception of Wertheim's experiments all endeavors to produce experimental gonococcal infection in animals were made by the use of organisms grown on ordinary serum media. He grew the organisms on a medium made from homologous serum, thus hoping to utilize the adaptive properties of these micro-organisms; however no attempt was made to increase the concentration of this homologous serum for the bacterial cultures.

Danyz (26) found rat serum highly bactericidal for anthrax bacilli but by growing these organisms successively in rat serum broth tubes he noted that they grew in more and more concentrated serum. The organisms thus immunized presented very different cultural and morphological characteristics. In a similar way he immunized anthrax bacilli to arsenical preparations.

With the above observations in mind I decided to grow gonococci under similar conditions previous to similar injection before concluding that the animals were absolutely immune to such infection. A laboratory strain of gonococcus was transferred from human blood agar to freshly made rabbit blood agar and this culture in turn was transferred in forty-eight hours to a second rabbit blood agar tube of the same blood concentration. Fifteen such transfers were made and the organisms were then tested to ascertain their resistance to fresh rabbit serum in the

following manner: A rack was prepared of small, clean, sterile test tubes containing unequal amounts of phosphate broth to which were added varying amounts of fresh rabbit serum to make the serum concentrations 1-2, 1-4, 1-8 to 1-128. The tubes now all contain the same volume. To each tube was added the same measured amount of gonococcus emulsion which had been made from a twenty-four-hour growth. As soon as each tube was inoculated it was shaken and a standard platinum loop full of the contents was plated on blood agar. The tubes were incubated at 37°C. and plates were made at intervals up to twenty-four hours. The plate cultures were then incubated for forty-eight hours and the colonies counted. By this method it was found that the bactericidal titre of rabbit serum for gonococci is about 1-75, that is the organisms are killed in thirty minutes in 1 part of rabbit serum to 74 parts of broth. This titre varies somewhat for the sera of different rabbits, 1-75 representing the average of four sera tested.

Table 1 presents the relative effects of rabbit serum on a strain of gonococci transplanted fifteen times on rabbit blood agar compared with the effect on a strain of gonococci grown on human blood agar. The comparison is made by the number of gonococcal colonies growing on blood agar plates after being exposed to various concentrations of fresh rabbit serum for different lengths of time. It is seen that a serum concentration 1-16 can be withstood by the rabbit serum strain for thirty-eight minutes, while the bactericidal action of 1-32 concentration is withstood for four hours and thirty minutes. The control organism did not live in any concentration of rabbit serum after a thirty-eight minute exposure.

Similar experiments made after the twenty-sixth successive transplant on rabbit blood medium show a still further increase in tolerance, since a two hour exposure in a 1-3 rabbit serum failed to sterilize and a nineteen-hour exposure in a 1-6 concentration did not kill all the organisms. These experiments were repeated on the thirtieth and also the thirty-fifth transplants on rabbit-medium, but the tolerance of these gonococci was the same as that following twenty-six transplants.

It would seem that this method of treating gonococci increases the tolerance for rabbit serum up to the twenty-sixth successive transplant but further transplanting neither increases nor decreases this tolerance.

Presuming that the natural immunity of rabbits to gonococcal infection is due in part to the bactericidal substances in the blood,

TABLE 1

Showing the relative lytic action of fresh rabbit serum on two cultures of the same strain of gonococci. Rabbit blood agar gonococcus fifteenth successive transplant. Human blood agar gonococcus sixth successive transplant—same strain. The numbers in each column represent gonococcal colonies appearing after 48 hours incubation.

	RABBIT SERUM—CONCENTRATION								SALT SOLUTION
	Whole serum	1-2	1-4	1-8	1-16	1-32	1-64	1-128	
Rabbit blood agar, gonococcus. Instantaneous exposure.....	24	4	10	76	16	52	28	11	62
Rabbit blood agar, gonococcus. 38 minute exposure.....	0	0	0	0	20	25	0	0	0
Rabbit blood agar, gonococcus. 4½ hour exposure.....	0	0	0	0	0	8	0	0	0
Rabbit blood agar, gonococcus. 22 hour exposure.....	0	0	0	0	0	0	0	0	0
Gonococcus from human blood agar. Instantaneous exposure.	0	0	6	10	16	60	20	6	20
Gonococcus from human blood agar. 38 minute exposure.....	0	0	0	0	0	0	0	0	0
Gonococcus from human blood agar. 4½ hour exposure.....	0	0	0	0	0	0	0	0	0
Gonococcus from human blood agar. 22 hour exposure.....	0	0	0	0	0	0	0	0	0

one may expect that neutralizing the effect of such substances by increasing the tolerance of the injected microorganisms for these substances might render animals injected with these organisms more susceptible to infection than animals injected with ordinary organisms.

To ascertain what effect if any such immunized organisms would have on rabbits, many animals were injected during the process of immunizing these gonococci and the protocols of a

few representative ones are here presented. For animal inoculation young rabbits under 800 grams in weight were used.

Rabbit 4. Injected intravenously, in 2 cc. of medium, the sediment from 8 cc. of rabbit kidney broth in which gonococci (tenth transplant on rabbit blood agar) had grown for forty-eight hours. At the same time a similar amount was injected into the right wrist joint, and twice this amount intraperitoneally. In five and a half hours a blood culture was negative and the peritoneal cavity positive for gonococci. The animal died in twenty-four hours after the injection and both the heart's blood and peritoneal fluid were sterile as were also the liver, kidneys and spleen. There was no evidence of infection about the wrist joint and the fluid was sterile.

Rabbit 2. Injected intravenously in 3 cc. of medium the sediment from 30 cc. of rabbit broth in which gonococci (tenth transplant on rabbit blood agar) had grown for forty-eight hours. Twenty-four hours after injection: animal sick, refuses to eat. Three days after injection: animal eats but is in very poor condition; lost 110 grams in weight; blood cultures negative. Five days after injection: lost 200 grams in weight; blood culture positive for gonococci; animal died 8 hours after the blood culture was made and no gross lesions were found post mortem. The blood, spleen, liver and kidneys were sterile. It is of considerable importance to note that on the third day after the intravenous injection the blood was sterile while on the fifth day a similar culture was positive for gonococci, leading to the conclusion that gonococci were not constantly in the blood stream for five days but were intermittently cast into the blood from some protected focus. Post mortem findings and cultures, however, failed to reveal the focus.

Rabbit 5. Injected intravenously in 3 cc. of medium the thirty hours gonococcus growth from 30 cc. of rabbit heart broth. The gonococci were the nineteenth transplant on rabbit blood agar. Eighteen hours after injection: rabbit very sick; does not eat; diarrhoea. Blood cultures sterile. Forty-eight hours after injection: animal dead. No post mortem findings. Blood, liver, spleen, heart and kidneys sterile.

Rabbits 10 to 17 inclusive. Injected intravenously with doses varying from 3 cc. to 5 cc. of medium containing gonococci grown for seventy-two hours on rabbit serum broth 1-16. Each cubic centimeter contained the growth from 10 cc. of medium. Gonococci from nineteenth transplant on rabbit blood agar. Blood cultures were made

from all of the animals twenty hours after the injection and but one (rabbit 15) was positive and it became sterile within forty-eight hours.

Rabbit 9. Injected intraperitoneally the sediment in 8 cc. of medium the forty-eight hour gonococcal growth from 50 cc. of rabbit kidney broth. Five hours after injection: blood cultures sterile; peritoneal culture positive for gonococci; peritoneal cavity distended; contains extracellular and intracellular organisms. Twenty hours after injection: blood cultures sterile; peritoneal culture positive for gonococci. Seventy-two hours after injection: blood cultures sterile; peritoneal cavity contains clear, serous fluid which is sterile. Animal made a complete recovery.

Rabbit 18. Injected intravenously 2 cc. of sediment containing the forty-eight hour growth of gonococci in 15 cc. of rabbit kidney broth. The gonococcus was the thirty-third transplant on rabbit blood agar. Two and a half hours after injection: blood cultures negative. Eight days later: injected intravenously 1 cc. medium containing the forty-eight hour growth of gonococci from 15 cc. of rabbit heart broth (thirty-fifth transplant). Twenty-four hours after second injection: left eye closed; purulent secretion; iris smokey with hyperemic appearance; whole eye looks edematous and larger than other eye. Blood cultures sterile. Forty-eight hours after second injection: left eye still closed; exudate not so profuse as the day before; moderate hyperemia of conjunctival and iris blood vessels; cornea and iris are smoky; pupil contracted to one-half the size of its fellow; blood culture sterile. Seventy-two hours after second injection: eye looks better but still hyperemic and smoky; pupil contracted. Five days after second injection: eye looks normal. Eight days after second injection: animal died; cultures from anterior chamber of eye gave few colonies of typical gonococci by culture and smear; the organisms could not be grown on transplants.

It was thought essential to increase further the tolerance of gonococci for rabbit serum before attempting further animal inoculation. A second series of experiments was made therefore using different concentrations of rabbit serum in broth as follows:

Gonococci were grown for forty-eight hours in rabbit serum broth 1-80. From this culture tubes of greater concentration of rabbit serum were inoculated and incubated for forty-eight hours. These

transplants were thus continued every forty-eight hours gradually increasing the strength of the serum. The order in which cultures were obtained is here outlined:

(1) Gonococci were transplanted from blood agar to rabbit serum broth 1-80.

(2) In forty-eight hours a transplant was made from the 1-80 culture to a 1-40 concentration.

(3) In forty-eight hours transferred from the 1-40 culture to a 1-10, 1-20, and 1-40 concentrations of fresh rabbit serum.

(4) In forty-eight hours there was good growth in all three tubes and a 1-5 concentration was inoculated from the 1-10 culture.

(5) Fair growth in the 1-5 tube in forty-eight hours, and a second 1-5 tube was inoculated from the 1-5 culture.

(6) In forty-eight hours there was a good growth in the 1-5 tube and a 1-2 tube was inoculated from it.

(7) Only a slight growth in forty-eight hours in the 1-2 tube, so transfers were made from it to a second one.

(8) In forty-eight hours there was moderate growth only but by five successive transfers an organism was obtained that grew readily on fresh rabbit serum 1-2.

(9) Tolerance could not be increased constantly beyond this point, although one strain of gonococci was obtained that eventually grew readily on whole rabbit serum.

It is apparent that gonococci readily develop a fastness for the gonococcidal substances contained in rabbit serum. This adaptive ability is not altogether unlike the tolerance acquired by typhoid bacilli for normal rabbit serum. Feiler (27) has found that these bacilli readily acquire fastness for immune serum and normal rabbit serum by growing the organisms on an active normal rabbit serum medium. This fastness is lost by one transplant on plain agar, but is present much longer when passed through bouillon.

The fastness developed by gonococci for normal rabbit serum is an acquired characteristic much more difficult to remove since it took twenty-five successive transplants of a gonococcus tolerant to 1-2 rabbit serum on human blood agar before this fastness was completely removed. There were no cultural or morphological changes noted between the serum fast and the normal gonococcus.

Gay and Claypole (28) noted, as have many others, that rabbits injected intravenously with typhoid bacilli would have positive blood cultures for a long time. The varying success of different observers undoubtedly means that all strains of typhoid bacilli are not equally resistant, that all rabbits are not equally susceptible, and that the organisms are not constantly in the blood stream but enter it periodically from a focus proved to be the gall bladder. The real typhoid carrier state could be produced only occasionally in rabbits by Gay and Claypole until they injected typhoid bacilli previously grown on rabbit blood agar where this condition would regularly follow. A strain of typhoid bacilli was produced which when grown on rabbit blood agar constantly caused the carrier state when injected into rabbits; while the same strain injected from plain agar produced no such condition.

The more serum fast gonococci were injected into rabbits in a manner similar to that previously described for the less tolerant organisms. The following protocol will suffice to explain the results:

Rabbit 33. The sediment in 1 cc. of medium of a forty-eight hour growth of gonococci from 15 cc. of rabbit serum broth (1-2) was injected intravenously. Forty-eight hours after injection the blood culture was sterile. Animal made complete recovery.

The finding of a positive blood culture forty-eight hours after intravenous injection has been previously reported but could not be obtained in these experiments by injecting other than the serum fast organisms and then only in three instances in thirty animals. The ordinary strain of gonococci could rarely be obtained from the blood twenty hours after injection and usually had disappeared within five hours. After intraperitoneal injections of serum fast organism it is usual to find gonococci in the peritoneal cavity for twenty-four hours. Blood cultures made at intervals between five minutes and forty-eight hours following intraperitoneal injections have always yielded negative results.

As previously mentioned one strain (no. 48) of gonococci grew readily in fresh whole rabbit serum and this was used to

inject intravenously a series of fifty rabbits. The blood was cultured in most animals but in none was a positive culture obtained more than forty-eight hours following the injection and in most instances the blood was sterile within twenty-four hours. Animals were injected with this organism intraperitoneally, intraarticularly and subcutaneously but no lesions were regularly produced; however many rabbits of this series developed a peculiar lesion of one or both kidneys not seen in other animals, normal or experimental. Since this lesion has not been produced regularly under the same experimental conditions and the organism has not been recovered from the lesions, more data must be obtained before it can be considered a gonococcal renal infection or even the result of such an infection.

In all 132 rabbits were injected in various ways with various strains of gonococci and except for the specific instances referred to, there has been no evidence of animal infection; indeed many deaths resulted, some immediately following the injection, others at intervals up to five days. All these however can be explained as the effect of the gonococcal toxin.

Believing that the bactericidal activity of rabbit serum had been largely overcome by increasing the tolerance of the bacteria used it seems probable that there must be other factors working to render rabbits immune to gonococcus infection. Tolerance to one serum in vitro does not necessarily mean tolerance to an homologous serum in vivo, since Peterson (29) has found that dog serum contains almost no bactericidal properties for anthrax bacilli yet dogs are highly resistant to this infection; rabbit's serum, however, is very bactericidal for anthrax bacilli yet these animals are readily susceptible to infection.

The high body temperature of rabbits may have some influence on organisms as heat sensitive as the gonococcus. This factor no doubt plays an important rôle in the rapid destruction of gonococci as shown by negative blood cultures five minutes after an intravenous injection; on the other hand there is no such rapid death of the organisms when injected intraperitoneally. Organisms thus injected can regularly be recovered after five hours and usually remain present twenty-four hours. If the body

heat were the only inhibiting agent, those organisms found in the blood stream and peritoneal cavity two and five days after an injection should be so adapted to this temperature that infection would result.

It must be conceded that gonococcal infection in rabbits has not been produced. The inconstancy of blood culture findings may be explained by the individual differences in the inhibitory activity of the various animals used but whether this resistance to infection is due to the bactericidal activity of the rabbit serum, to the deleterious effect of the body heat of rabbits or to both it is impossible at present to say. It may be that either the mechanical or chemical action of fixed tissues acting alone or in conjunction with the previously mentioned factors render the rabbit non-susceptible to gonococcal infection.

CONCLUSIONS

1. Rabbit serum has a marked bactericidal action on gonococcal cultures. The titre varies for different rabbits but averages approximately 1-75.

2. Gonococci readily adapt themselves to such bactericidal substances and by growing them on gradually increasing strengths of fresh rabbit serum broth gonococci will readily grow on serum broth 1-2.

3. One strain of gonococci adapted itself to whole rabbit serum in which it grew readily.

4. Successive transplantation of gonococci on rabbit blood agar increases the tolerance of these organisms for rabbit serum up to the twenty-sixth transfer. Further transplantation neither increases nor decreases the tolerance already acquired.

5. This serum fastness of gonococci seems highly persistent since it took twenty-five successive transplants on human blood agar to cause its complete disappearance.

6. The serum fast gonococci remain longer in the blood stream of a rabbit than an ordinary strain of gonococci. Positive blood cultures were obtained forty-eight hours after intravenous injection on three occasions and in one animal five days after injection. Ordinary gonococci do not so behave.

7. Positive blood cultures were not obtained after intraperitoneal injections of gonococci. The organisms could usually be recovered from the peritoneal cavity up to twenty-four hours but rarely later.

8. There is no conclusive proof of gonococcal infection having taken place in any of the 132 rabbits injected. Typical iritis developed in one animal twenty-four hours after intravenous injection. Gonococcus-like organisms were recovered but not completely identified. This lesion could not be reproduced by exactly similar methods.

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REPAIR OF URETHRAL DEFECTS BY TUBULAR GRAFTS OF VAGINAL MUCOSA

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There are several methods of repair for loss of substance in the urethra. One of the most interesting and novel among these is accomplished by grafting the mucous membrane of the vagina. This method was originated in 1910 by Tanton in my service at Laennec with my collaboration. The result obtained was excellent.

Since that time I have had several opportunities to make use of the method for war wounds. Two of the results have been followed now long enough to show the ultimate result. In the following paper I shall report my three cases (the only ones I have any knowledge of) and then study the technique, the results and the indications of this operation.

Case 1 (Legueu and Tanton (1)). Patient thirty-four years of age, showed as a result of several attacks of gonorrhoea, multiple urethral strictures. In 1909 he had complete retention of urine, and thereafter an internal urethrotomy was performed, followed by electrolytic dilatation. The first dilatation caused no great reaction; the second, after an interval of eight days, consisted, according to the patient in the introduction of a rather large sound which was painful and was followed by electrolysis for twenty minutes and a profuse hemorrhage. Fever ensued and an abscess formed at the penoscrotal angle which opened spontaneously, leaving a large fistula, the urethral opening being 1.5 cm. in diameter. The patient entered Laennec in this condition. Examination showed that all the urine was passed through the fistula, the penile urethra being totally occluded from fistula to meatus, the meatus itself being completely obliterated. This part of the urethra was palpable as a fibrous cord as thick as a goose quill. It was proposed to reconstruct the penile urethra by a tubular graft of

vaginal mucous membrane. The operation was planned in three steps.

1. Temporary diversion of the urinary stream.
2. Application of the graft with closure of the penile fistula.
3. Closure of the temporary fistula.

As a matter of fact four operations were necessary since a fistula resulted which required a special operation to close it.

1. The first step was a perineal urethrotomy performed on May 20, 1910.

2. Fourteen days later the perineal drainage being good, the plastic operation was attempted.

The sclerotic urethra was excised from the fistula to the base of the glans penis through a longitudinal incision underneath the penis. The glans was tunnelled by a trocar, the incision being large enough to take a 26-F sound. The outer end of the urethra, at the point of fistula, was freed for about 1.5 cm. Meanwhile, M. Legueu was performing a colpo-perineorrhaphy, in the course of which he excised a rectangular segment of vaginal mucosa. This was dropped for a few moments in warm artificial serum, then rolled about a 26-F bougie its edges caught with fine cat gut so as to form a tube about 8 or 9 cm. long. The bougie carrying the graft was then introduced into the tunnel in the glans penis and placed in the gutter left by the excision of the anterior urethra, care being taken to place the line of grafted suture in the angle of the two corpora cavernosa. The end of the bougie was introduced into the urethra and this sutured end to end to the graft by an interrupted cat gut suture. The superficial tissues were united in two layers over the graft and a small drain left in place, the outer extremity of the graft being sutured to the meatus.

The bougie was withdrawn on the morning of the third day. The following day the patient's temperature rose and infection appeared at the point of fistula resulting in a breaking down of the graft and a fistula the size of "a twenty-centime piece." This gradually contracted to the size of a small bean. Meanwhile at the meatus a small slough appeared as a result of the pressure of the bougie. This destroyed the graft for a depth of about 5 mm.

June 14, a 15-F bougie passed readily into the urethra.

June 16, a 19-F bougie readily introduced.

Thereafter dilatation was continued every third day up to 26-F.

3. On July 7, under cocaine anesthesia the fistula was closed by a urethrorrhaphy by apposition, the apposed flaps being held in place by Duplay's tubes.

On July 12 the sutures were removed and the fistula found completely closed. Dilatation was then continued by the passage of 25-F sounds.

On July 21 the perineal fistula was closed under local anesthesia, the perineum being sutured in layers. An indwelling catheter 23-F was left in the urethra for several days.

On August 2, the patient left the hospital, his canal taking a 25-F bougie readily.

Since this time the patient is at work but comes to Paris once a week for dilatation. Bougies 25 and 26 and sounds 26 and 27-F are passed readily. The urinary stream is normal, the operative result excellent.

At first adhesion of the skin to the urethral graft produced a slight chordee but this has disappeared.

Case 2. Urethral wound by shell fragment. Repair by graft of vaginal mucosa. Ultimate result excellent.

"V," aged twenty-four years, wounded September 28, 1915, entered our clinic June 12, 1916, for a urethral wound. The projectile had perforated the lower part of the buttock, fractured the ischio-pubic ramus, destroyed the penile urethra and wounded the right testicle. The patient was transferred to the hospital at Arc, where, on September 30, 1915, the right testicle was removed and suprapubic puncture to relieve the retention of urine obtained a litre. Several days later at another hospital, a suprapubic fistula was established. A bougie introduced into the meatus was arrested in front of the fistula by complete occlusion of the canal, while a bougie introduced into the fistula entered the bladder without difficulty.

January 21, under chloroform, excision of cicatrices obliterating the urethra and suture of the two urethral extremities to the skin at a distance of about 2.5 cm. from each other. Several weeks later, the urethral wounds having healed, restoration of the canal by means of a vein was attempted since the loss of substance was not great. On April 5, 1916, under chloroform, 8 cm. of the internal saphenous vein was excised and threaded it over a bougie to which it was affixed by two ligatures. Then, by means of a trocar, the canal was tunneled under the skin of the penis from the anterior to the posterior stoma of the urethra. Into the canal thus opened, the sound with its venous transplant was introduced; the sound was then withdrawn and the graft sutured to the urethral extremities by fine interrupted sutures, these urethral extremities having previously been separated from the

skin. Unfortunately the venous transplant did not take and was found several days later in the dressings. The transplantation of mucous membrane was then decided upon. On June 5, 1916, during the course of a perineorrhaphy, a rectangular bit of vaginal mucous membrane 6 cm. long and 3 cm. wide was removed. While I was concluding the perineal operation, my assistant, M. Morel, thinned down the transplant to the thickness of a franc piece and rolled it about a no. 18 bougie, suturing it with interrupted sutures of very fine silk with fine needles. The two extremities of the cylinder of mucous membrane were tied to a catheter by two cat gut ligatures with ends left long. During all these steps the graft was irrigated with warm serum and then dropped into a basin of the same.

Meanwhile the patient was put under an anesthetic, the penile urethra freed for about 1 cm. from each of its separate extremities, between which the superficial tissues were again tunneled from one orifice to the other by means of a trocar and canula. The trocar was then removed and an attempt made to introduce the catheter and graft into the canula, but the graft would not enter. It was therefore slipped off the bougie and gently introduced into the canula. This was then withdrawn and the graft sutured to each end of the divided urethra by five sutures of very fine silk and the skin united over the graft. No retained bougie or catheter was left in the urethra.

The graft took well and bougies were passed after a few days. On September 22, 1916, under chloroform, M. Morel closed the two fistulae and thereafter the urethra held completely and dilatation was continued regularly.

On October 30, 1916, the patient passed a no. 18 bougie readily. The fistula remained closed. The result was excellent. Since that time the patient has remained as an orderly in my service and I see him from time to time. His urethra is soft and takes a no. 19 bougie readily. I demonstrated him to a delegation of American surgeons on April 22, 1918.

Case 3. Extensive wound of the scrotal urethra. Closed by transplantation of vaginal mucous membrane. Good result.

Private "B," twenty-four years of age, wounded March 5, 1916, by a bullet which perforated the internal surface of the left buttock, passed through the scrotum, injured the left testicle and issued through the right buttock. The patient had retention of urine for forty-eight hours which was relieved by suprapubic cystostomy on March 7. He entered the clinic April 1, 1916, with the cystostomy wound and an in-

cision in the left side of the scrotum through which the testicle had been removed. There was a suppurating wound of the right buttock. Liquid injected into this wound issued through the wound in the scrotum. There was therefore a urethral wound communicating with the scrotum and the bladder.

On April 20 the bladder fistula had healed but no instrument could be introduced into the bladder through the urethra.

May 29, 1916, the wound had completely cicatrized but the urethra was obliterated by a cicatricial stricture. The patient was ordered to leave our hospital but returned in the month of June of the same year requiring an operation to open his urethra.

On June 23, 1916, operation under chloroform by M. Legueu. Median perineal scrotal incision down to the urethra which was opened in front of the stricture and sutured to the skin at the peno-scrotal angle. Behind this point the urethra was obliterated for a distance of 5 cm. This portion of the urethra was excised and the posterior orifice sutured to the skin of the perineum, the wound between the two orifices being partly closed and packed.

On the tenth day the sutures and packing were removed and dilatation begun two days later. At the end of a month a 25-F sound passed readily and the two urethrostomies had healed.

On September 18 a piece of vaginal mucous membrane 5 cm. long was excised and dropped into warm artificial serum. My assistant, M. Morel, fashioned it into a cylinder about a 19-F bougie.

The space between the two urethrostomies was then tunneled with a curved trocar and canula. The trocar was removed and an attempt to introduce bougie and graft into the canula failed. This was removed therefore and the graft placed in position and fixed by interrupted sutures to the two cut ends of the urethra, the whole being buried by closure of the skin orifices of the urethrostomies.

On October 1 a bougie 12-F was passed and thereafter dilatation continued every two or three days.

In December the cystostomy tube was removed. A 19-F bougie passed readily with a slight hitch in the anterior part of the urethra. There were two small fistulous openings at the points of urethrostomy.

In January dilatation became difficult and an 18-F sound passed with difficulty. The 19-F bougie passed more readily.

On March 21 a plastic operation was performed for the closure of the two fistulae. Indwelling catheter. Thirteen days later the fistulae persist. Dilatation was continued. On May 7, 1917, a second at-

tempt was made to close the two fistulae; indwelling catheter 17-F. This operation was successful although a pinpoint fistula persisted. In September an internal urethrotomy was performed under chloroform anesthesia and the stricture at the juncture of the graft and the urethra divided. On November 15, 1917, a no. 19 bougie could be introduced. The result is good, the caliber of the urethra satisfactory. It is possible, if the man had been less rebellious and alcoholic, better results might have been obtained.

TECHNIQUE

Before describing our present technique we must state certain general preliminary conditions essential to the success of the operation. They are the following:

1. The resection must be preceded by a temporary urethrostomy which involves the suture to the skin of both ends of the wounded urethra; upon the result of this operation depends the functional success of the ultimate result. Thus one of our patients had a stricture at the union of the posterior portion of the graft and the urethra.

After making this urethrostomy, several months must elapse before applying the graft in order to work on uninfected tissues. The orifices must also be dilated in order to prevent such a stricture as occurred in the above case.

2. The second preliminary requirement is a suprapubic cystostomy. It is preferable to establish this before the urethrostomy. Perineal diversion of the urine is not satisfactory since it leaves a more or less infected wound near the point of grafting.

3. Finally, in order that the graft shall take, the tissue should be prepared by tunneling. This is a general principle applicable to all grafts of foreign tissue in the urethra which should always be made beneath the skin. When transplanting veins we have had several failures because of placing them beneath the skin incisions. The tunneled canal cannot break down. Thus one of the causes of failure is removed.

These fundamental conditions being realized, the operation is performed in the following steps:

a. *Excision of the graft.* A woman requiring colpoperineorrhaphy, preferably otherwise healthy and not syphilitic, is anesthetized and from the posterior wall of the vagina a flap of vaginal mucosa is resected the length of which should equal the length of the portion of the urethra to be replaced and its width sufficient to surround completely a 17- or 18-F bougie. While this portion is being completed an assistant prepares the graft which is kept moistened with artificial serum. The raw surface of the graft is first denuded of all cellular and fatty tissue. It is necessary to make it as thin as possible for the epithelial surface is all that is of value. The rest is only accessory and the graft will always be placed in a canal which is rather tight for it. Next the assistant sutures the vaginal mucosa about a 17- or 18-F olivary bougie with several extremely fine silk sutures. The two ends of the graft are ligatured about the bougie with cat gut sutures whose ends are left long to assist in threading the graft into the perineal tunnel.

b. *Tunnelization.* The patient is anesthetized and placed in the lithotomy position. The two ends of the urethra are freed from the skin. A special trocar provided with several canulae of various lengths and calibers is then plunged into one of the urethrostomy wounds and brought out through the other. The trocar is then withdrawn leaving the canula in place.

c. *Application of the graft.* This step is always a delicate one. The graft is always too big for the trocar for the latter cannot be large enough without endangering the vitality of the skin. It may be necessary to remove the graft from the bougie and to introduce it without any guide into the canula. This is done by passing a small platinum hook through the canula to catch one of the cat gut sutures and draw it through with the graft following. The canula is then withdrawn and the graft is in place.

d. *Suture.* The two ends of the urethra are very accurately sutured to the ends of the graft by a series of very fine silk interrupted sutures. This must be placed accurately but with as little manipulation as possible in order not to diminish the

vitality of the graft and thus favor sloughing by traumatism and pressure.

e. Closure of the fistulae. The two cutaneous fistulae are closed by dissection of the underlying tissues and suture of the skin over the urethra with silk worm gut.

After treatment. The perineal dressing is left in place for eight days. There will then often be found a slight breaking down of the tissues at the points of union of the graft and the urethra but in none of our cases has the graft been eliminated. Eight days later a small bougie is very gently introduced and thereafter the urethra is dilated progressively until bougies can be readily passed. Thereafter the caliber of the canal is maintained by bougies or sounds. There are several subsequent operations required but these are slight secondary ones of little importance and which merely prolong the duration of treatment.

RESULTS

The duration of treatment is always long because there is often a wound of the urethra which takes several months to heal, then urethrostomy and finally the terminal secondary operations to close the fistulae. Our patients have remained for more than two years in the hospital. Nevertheless the perfection of the results is in proportion to the patience of preparation and the care with which urethrostomy is performed. If this operation is satisfactory the grafting will probably achieve its result. In order to make a urethrostomy satisfactory several operations may be required.

Our results were twice excellent and once good. Our case 3 was extremely rebellious and alcoholic and interfered with his treatment; the second case on the contrary achieved an excellent result and the patient, who remained as an orderly in the hospital, is in most satisfactory condition. The first case is also a perfect result.

It must be recognized that the graft of vaginal mucosa serves merely as a canal. The graft itself does not form the new canal. We have unfortunately not been able to conclude certain experi-

mental researches begun with our assistant, M. Morel, at the beginning of the war, but we have satisfied ourselves that these grafts only serve as a scaffolding upon which the epithelium of the old canal is able to grow. The graft is eliminated little by little as the new urethra substitutes itself in its place. The same rule holds for venous transplants and is indeed a general law in reference to all transplants which are actually foreign bodies. The only question, therefore, is what is the best kind of graft for repair of extensive loss of substance in the urethra. We believe that vaginal mucosa is among the best and gives excellent results.

INDICATIONS

It would be premature to attempt to lay down precise indications for this operation at the present moment but we can formulate certain provisional rules.

If the loss of substance is slight no graft is required. Unfortunately the wounds of war usually involve so great a loss of substance that end to end suture of the urethra is impracticable. But when the loss of tissue is not so great the simplest operation consists in a skin autoplasmic. On the other hand if the loss of substance is very great the skin is not available since it may result in urethrocele, of which we have seen several examples. For such cases when the loss of substance is 3 or 4 cm. in length a graft of vaginal mucosa or vein should be employed but the vaginal graft being more successful, should be preferred. But it is to be noted that our cases are few and our technique is likely to be modified by subsequent experiences in war surgery. Be this as it may the grafting of vaginal mucosa appears to be an excellent method and warrants great hopes for its future usefulness.

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AN UNIQUE TYPE OF URETHRAL OBSTRUCTION

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The literature of dilatations of the urethra resulting from various types of obstructions and of urethral diverticula has been reviewed very carefully by Watts and more recently by Englander.

The following case is reported on account of the unique type of obstruction which resulted from traumatism and to consider the surgical procedure which brought about a relief of the obstruction and a successful restoration of the urethra.

Patient, age thirty-eight, married, was admitted to the Hospital of the Good Samaritan on October 7, 1916. The history in brief was as follows:

On September, 1916, while at work he fell 12 feet striking the perineum on the corner of a box. He did not seem to be greatly injured at that particular time but for about three hours had a desire to urinate without being able to do so. After an extreme effort bright red blood was passed. A hard mass then appeared in the perineum and in the scrotum. He consulted a physician who sent him to a hospital and blood and urine were passed from the urethra for two days. Hot compresses were applied to the mass in the perineum and he seemed to improve. He stayed in the hospital nine days and then returned to work but still had considerable difficulty in passing urine. One week after leaving the hospital, the scrotum was so swollen and urination so difficult that an opening was made into the right side of the scrotum and when the patient was first seen by me, urine was passed only through this opening.

Examination showed a well nourished man who did not in any way appear ill. The entire scrotum was tense and filled out, the right side being somewhat larger than the left. This swelling extended down to the mid-portion of the perineum. There was a small opening on the under surface of the scrotum a little to the right of the midline from

which urine escaped. Rectal examination was negative. Suprapubic percussion showed only slight distension of the bladder. A coude catheter readily entered the bladder, withdrawing 300 cc. of bluish urine. When slight pressure was made over the scrotum thick grayish purulent material escaped around the catheter.

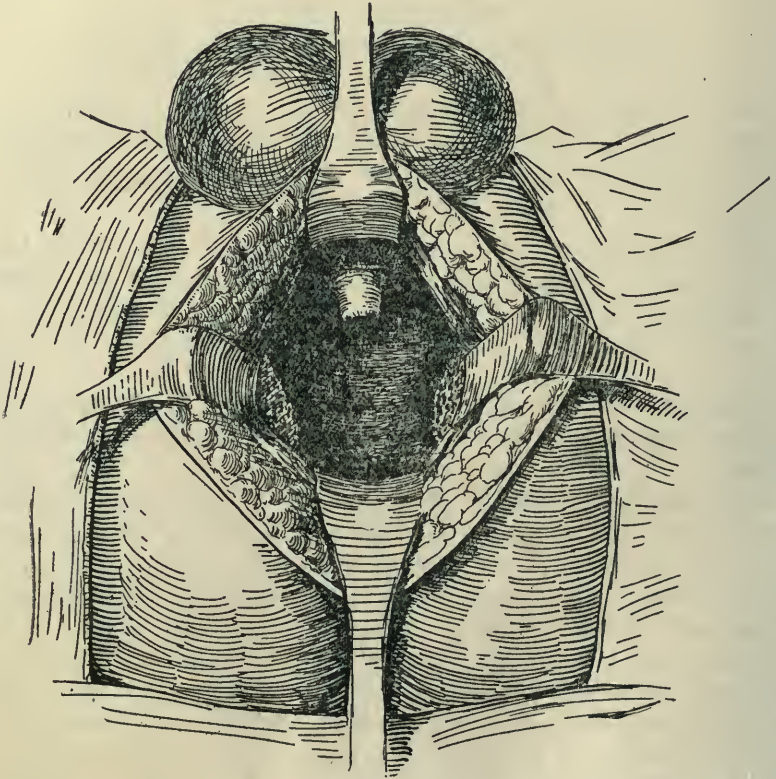


FIG. 1. SHOWING VIEW OF PERINEAL SAC AND THE TORN URETHRA PROJECTING INTO IT

The perineum was opened through a midline incision and about 30 cc. of purulent and broken down tissue material was evacuated. Patient made a very good recovery and the perineal wound closed on the fourteenth day. This patient was advised to return for dilatation of the urethra but reported for only two treatments and then was not seen until May 14, 1918, two years later, at which time he was able to urinate only a few drops at a time and this principally by bringing

pressure to bear in the perineum with the hand. The patient looked distinctly ill.

Examination showed a large, tense, fluctuating mass in the perineum about the size of a large egg. This mass also seemed to extend for-

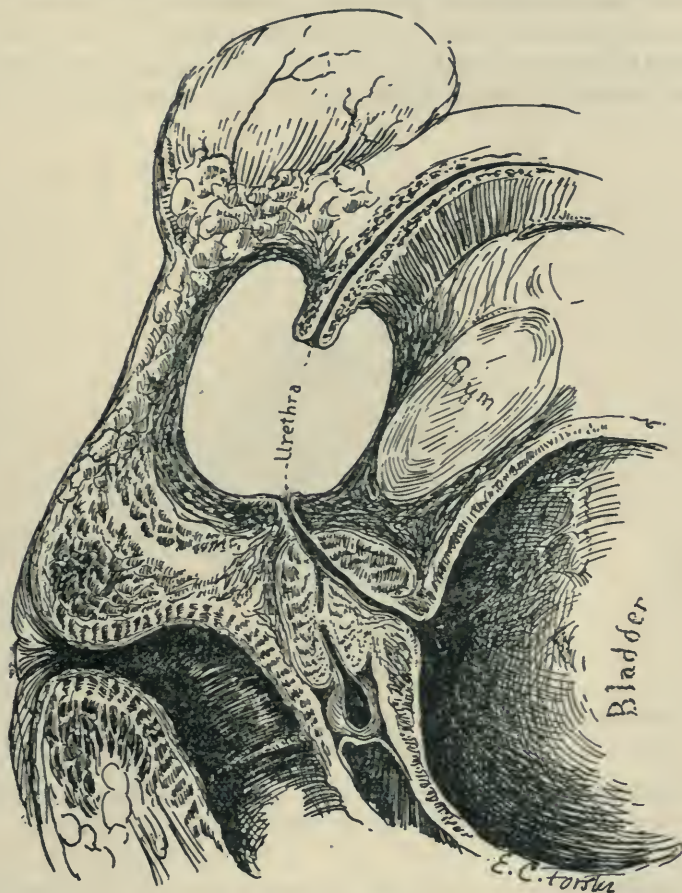


FIG. 2. LATERAL VIEW OF PERINEAL SAC

ward into the region of the scrotum. A catheter could be passed very easily into what was definitely a sac and 80 cc. of very purulent urine could be withdrawn after which the swelling in the perineum would disappear. With a silver catheter it was possible to pick up the proximal end of the urethra and enter the bladder withdrawing 400 cc. of

purulent urine. Upon attempting to urinate the sac would first fill at which time he would suffer severe pain. By pressure in the perineum a drop or two of urine could be forced out of the urethra.

The urethral obstruction did not seem to be a stricture because large sized instruments could readily be passed into the sac. It was thought advisable for his general condition to carry out catheter drainage of the bladder and for this purpose a coudé catheter was introduced into the bladder by means of a stilet and fastened in by adhesive tape

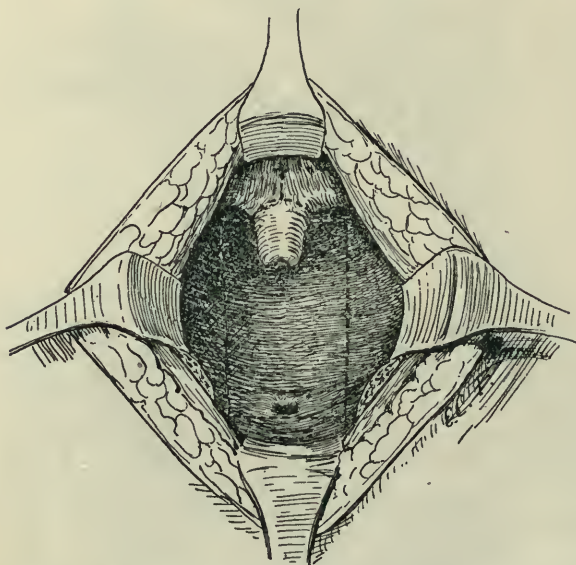


FIG. 3. PROJECTING PORTION OF THE URETHRA PULLED DOWN AND CUT OFF ALONG DOTTED LINE

A portion of the roof of the sac was then outlined as shown by dotted lines and used for the reconstruction of the perineal portion of the urethra.

as for preliminary treatment for prostatectomy. The patient's general condition improved very rapidly under this treatment and one or two attempts were made to determine whether he would be able to void if the catheter were removed. In no instance was he able to do so. The perineal sac always became greatly distended and complete retention of urine occurred.

Operation, June 18, 1918. The patient was placed upon the table in exaggerated lithotomy position. A sound was passed through the

urethra and a midline incision was made in the perineum. Upon opening the perineum down to the urethra a most striking condition was encountered. A sac measuring 6.5 cm. in length and 4.5 cm. in breadth was found to occupy almost the entire perineum. The sac was lined with glistening mucous membrane throughout and extended up around the urethra into the region of the scrotum on either side. Portions of the bulb were found on either side of the sac as shown in figure 1. The striking feature was the condition of the distal end of

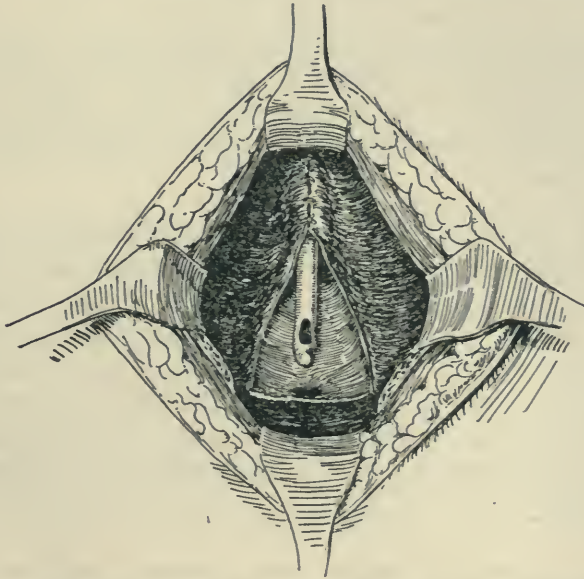


FIG. 4. RECONSTRUCTION OF THE URETHRA ABOUT A CATHETER

The rest of the mucous membrane lining the sac has been denuded.

the urethra which evidently had been torn directly across and which now projected into the sac for a distance of 1.5 cm. This end of the urethra was not indurated and contracted by scar but was soft and dimpled and readily admitted large instruments by way of the urethra but it could be well seen that the relation of this projecting urethra to the sac was the same as the relation of an enlarged prostate to the bladder. An instrument could be easily passed through the prostatic urethra into the bladder. In considering the type of operation it first occurred that the incision could be made around the base of the

projecting urethra and this portion of the mucous membrane pulled off, thus inverting the outer covering and a urethra of sufficient length made to allow the mucous membrane to be sutured to the opening near the membranous urethra. The danger of the graft breaking down however after the entire lining of the sac had been denuded and the danger of recurrent obstruction thereby resulting ruled out an attempt to restore the urethra in this way.

What was done was to pull down as far as possible the distal portion of the urethra and to cut this off as shown in dotted line of figure 3. Then to turn up a flap from the lining of the sac as shown in figure 4, and to denude the rest of the mucous membrane lining the sac. The tissues of the perineum were then brought together snugly about the newly formed urethra. The drainage tube was removed on the tenth day and the patient has voided urine since through the urethra in a large sized stream.

This case presented practically a secondary bladder in the perineum with almost complete retention developing within this sac. The cause of the obstruction is rather unique in that most dilatations of the urethra and diverticula have formed back of a contracture or stricture of the urethra and in one of my cases in which a large diverticulum had formed in the perineum the sac was to all practical purposes obliterated by dilatation of the urethra. In this case it is evident that dilatation could not have been of value.

TUBERCULOSIS OF THE MESENTERIC LYMPH GLANDS AS A CAUSE OF URETERAL OBSTRUCTION

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The diagnosis of tuberculosis of the mesenteric lymph glands is extremely difficult and in reviewing ninety-five cases of this condition found in the literature, very few were correctly diagnosed before the exploratory operation. Acute or chronic appendicitis was the most common diagnosis although many of the cases were operated upon for intestinal obstruction. The diagnosis in one instance was multiple uterine fibromata while in two others the operation was performed for "abdominal tumor." In one case the patient was in collapse from abdominal pain, the exploratory operation revealing a large tuberculous gland with mesenteric thrombosis. In none of these ninety-five cases is there any mention of tabes mesenterica as an etiological factor in the production of symptoms referable to the urinary tract. It is thought interesting therefore to report the following cases which were referred to the writer for right renal colic.

Case 1. Female, aged twenty-eight; domestic

History. One year ago had pain in the epigastrium and right lower quadrant for which an appendectomy was done, the appendix showing a chronic inflammatory process. Her pain continued however with the addition of indefinite right lumbar attacks and bladder irritability.

Examination. The patient was poorly nourished and very nervous. Upon abdominal examination there was marked tenderness in the right side. There was no distension, no moveable dullness and no palpable mass. The right kidney could be felt above the area of chief tenderness and was apparently normal in size. There was no fever, no leucocytosis and the bladder urine was normal.

Cystoscopy. The bladder was normal in every respect. Both ureters were readily catheterized, the catheters meeting no obstruc-

tion. Six milligrams of phenolsulphonphthalein injected intravenously appeared on each side in four minutes, the output for fifteen minutes being 15 per cent from each kidney.

Roentgenogram. The exposure was made with the catheters in place. As shown in figure 1 a large oval shadow is seen adjacent to the right ureter and on a level with the iliac crest.

Diagnosis. Large calcified tuberculous mesenteric lymph gland which at times by external pressure on the right ureter causes temporary obstruction and pain referable to the urinary tract.

Operation. Through a right rectus incision the calcareous gland was found in the mesentery of the ascending colon and removed. Other smaller glands were felt but as they were apparently causing no trouble they were not interfered with. Wound closed without drainage.

Case 2. Female, aged sixteen; school girl.

History. For two days prior to admission the patient had suffered from attacks of acute pain in the region of the right kidney, the attacks being accompanied by urinary frequency.

Examination. A poorly nourished, pallid girl. Lungs and heart negative. The abdomen shows no distension, moveable dullness or masses. The right kidney is readily palpated and feels normal. There is distinct tenderness over the right lower abdominal quadrant. Temperature, leucocytes and urine normal.

Cystoscopy. Reveals no abnormalities. Upon ureteral catheterization the catheters pass readily into the pelvis of either kidney. Phenolsulphonphthalein appears in each urine in five minutes, the output for fifteen minutes being 15 per cent from each kidney.

Roentgenogram. This was taken with the catheters in position and reveals two shadows above and to the right of the right catheter as shown in figure 2.

Diagnosis. Calcified tuberculous mesenteric lymph glands causing occasional obstruction to the free drainage of the right ureter.

Operation. Through a right rectus incision the calcareous lymph nodes were found in the mesentery of the ascending colon and removed.

Case 3. Female, aged nineteen; stenographer

History. Always delicate although never seriously ill. Four days before admission she was taken suddenly ill with acute pain in the region of the right kidney which radiated downward. There was

urinary frequency and tenesmus. The pain was suddenly relieved and the patient passed about a "pint of urine." She was sent into the hospital with the diagnosis of right ureteral obstruction causing intermittent distension of the renal pelvis.



FIG. 4. THE CALCIFIED LYMPH GLANDS SHOWN IN FIG. 3, AFTER OPERATION, SHOWING DIAGRAMMATICALLY THEIR RELATION TO THE URETER AS FOUND AT OPERATION

Examination. Showed a fairly well nourished, pale girl. Heart and lungs negative. Upon abdominal examination there were no masses or moveable dullness but over the right kidney area there was distinct tenderness, yet the kidney could be palpated and seemed

normal in size. There was no abnormal enlargement of the cervical, axillary or inguinal glands. There was no fever, no leucocytosis and the urine was free of pathological elements.

Cystoscopy. Revealed a normal bladder. Upon ureteral catheterization the separated renal function as determined by the phenol-sulphonphthalein test showed an appearance time of four minutes and an output of 10 per cent from each side in ten minutes.

Roentgenogram. This was taken with the right ureteral catheter in place and, as shown in figure 3, shows two shadows, one tangent to the catheter.

Diagnosis. Calcified tuberculous mesenteric lymph nodes pressing upon and obstructing the right ureter.

Operation. Through a right rectus incision the glands were removed from the base of the mesentery of the ascending colon. Their relation to the ureter was reproduced with an ureteral catheter after removal as shown in figure 4. There were other small glands felt in the mesentery but none seemed to be so located as to cause any mechanical difficulty so they were not removed.

GENERAL DISCUSSION

The diagnosis of the three cases just cited was greatly facilitated by the presence of the mineral deposit in the lymph nodes sufficient to cast a shadow to the X-ray and it is questionable whether in the absence of calcification a correct diagnosis would have been possible. In looking over the records of cases referred to the writer for mild symptoms of right ureteral obstruction and reported normal urologically, it is probable that some of them may have had intermittently obstructing lymph nodes which were not demonstrated.

Tuberculosis of the mesenteric and retroperitoneal lymph nodes is doubtless quite as common as tuberculosis of the cervical and peribronchial glands and like all tuberculosis is most common in youth. When the movable dullness and abdominal distension of tuberculous peritonitis are present, the condition is easily recognized but the less extensive involvements are usually overlooked. Of the 97 reported cases reviewed by the writer, in none of them is there any mention of symptoms refer-

able to the urinary tract. It is thought interesting therefore to present briefly the clinical picture of this pathological condition.

SYMPTOMS

In order of frequency the symptoms of the reported cases are as follows: general debility, general abdominal pain, pain in the lower right abdominal quadrant, indigestion, vomiting, abdominal distension, abdominal night pain in children, constipation and obstipation. To these symptoms should be added bladder irritability and right renal and ureteral pain.

EXAMINATION

Like all cases of chronic tuberculosis, these patients are usually below normal weight, color and strength. The abdomen in children is usually distended. Tenderness is general and of moderate degree but is usually most marked over the lower right quadrant. The movable dullness due to free fluid occurs only when the disease involves the peritoneum. Tumor masses were palpated in 15 per cent of the cases. In one case the glands could be palpated rectally and in another they were felt on vaginal examination. Involvement of the cervical or inguinal glands was noted in three cases. In eleven cases where the skin test was reported, ten gave a positive reaction. A leucocytosis of 13,000 is the highest recorded. It is usually normal. Talbot reports the presence of an excessive amount of fat in the stools in seven out of eleven cases occurring in children. The diurnal temperature is usually normal with a moderate evening elevation. The glands can be demonstrated by the X-ray when they have undergone sufficient calcareous change.

TREATMENT

As in all cases of tuberculosis the mainstay of the treatment is hygienic. When the glands are interfering mechanically with the normal function of the intestines, blood vessels or ureters, they should be removed surgically.

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PLATE 1

FIG. 1. Large calcified lymph gland lying tangent to right ureter and causing obstructive symptoms.

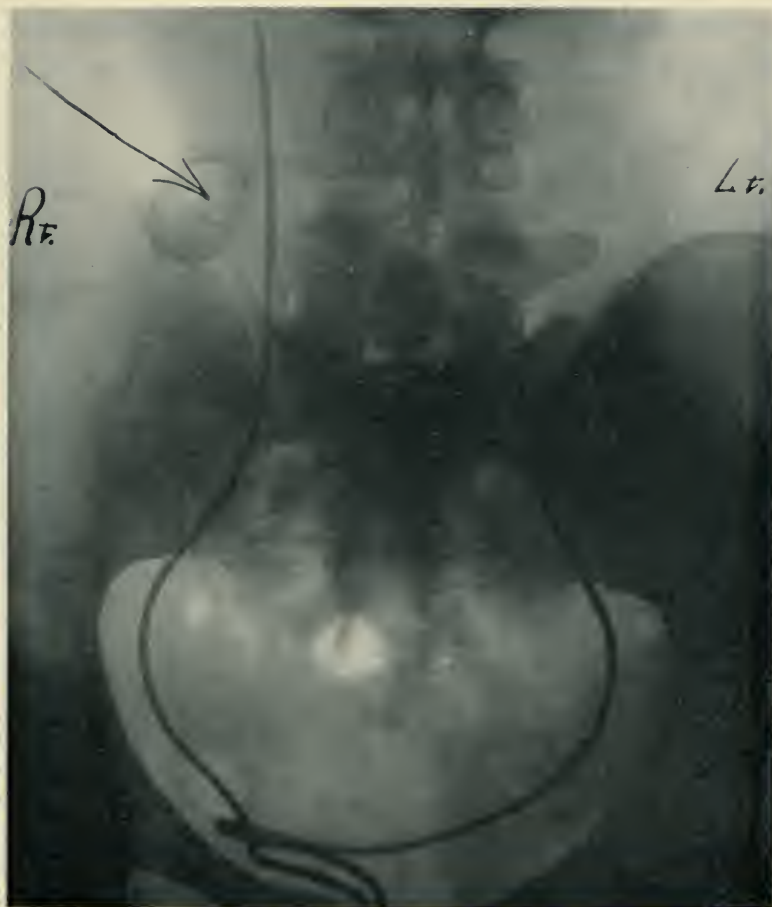


FIG. 1

PLATE 2

FIG. 2. Two calcified lymph glands in region of right ureter causing symptoms of ureteral obstruction of ureter at times.

FIG. 3. Two calcified lymph glands in region of right ureter causing symptoms of ureteral obstruction.



FIG. 2



FIG. 3

EXPERIMENTAL PYELITIS IN THE RABBIT

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From a study of the literature as well as from our own experiments carried on with organisms isolated from human pyelitis cases, it is evident that only very occasionally do organisms localize in the kidney after intravenous injection unless there is some obstruction in the course of the urinary tract. The experiment of Hess (1), of Cabot and Crabtree (2) and of many others show that bacteria pass through the kidney in large numbers without affecting that organ. From the results of our experiments with colon bacilli isolated from human pyelitis cases, we had come to practically the same conclusion. In striking contrast to all this work are the results of this experimental study, in which infections of the kidney were produced after intravenous injections of the organisms in about two-thirds of the animals.

In like manner a study of the literature concerning ascending infection of the urinary tract, other than tuberculous shows that without some accessory factor it was practically impossible to produce an ascending infection of the kidney. Hess (1) in his experiments was able to produce an ascending infection by injecting turpentine into the bladder before injecting it with colon bacilli. Sweet and Stewart (3) showed that when the ureters were implanted into the intestinal wall, an ascending infection of the kidney occurred. Cabot and Crabtree (2) are inclined to the opinion that even when colon bacilli are carried in the lymph stream from the bladder, they reach the kidneys by way of the blood stream rather than by way of the lymph channels.

Eisendrath and Schultz (4) obtained positive cultures from the kidney in a number of their experiments but never macroscopic changes in the kidneys indicative of involvement of the

pelvis or substance of the kidney. In marked contrast to these observations are the results of our experiments. In 10 out of 15 intravesical injections we were able to demonstrate definite macroscopic lesions of the kidneys. In all of the experiments the urine was previously controlled by culture and by microscopic examination.

The results in these two series of experiments are so at variance with the work of this kind reported in the literature that we wish to report in detail the findings of all our experiments. The histological study of this large series of rabbit kidneys has shown us as others have previously observed, that the rabbit is subject to spontaneous kidney lesions in no small number of cases. In 10 of the animals studied, we were able to demonstrate lesions of the kidney that were definitely of longer standing than could result from our injections. Of the 10 animals showing chronic changes, 4 (rabbits 76, 63, 68 and 42) presented also acute lesions, from which colon bacilli were isolated, so that there can be little question that there was a double process in these 4 animals. In the other 6 (rabbits 31, 32, 40, 53, 57 and 87) only the chronic processes were observed. These chronic changes were manifested by focal increase in connective tissue and in small areas of lymphocytic infiltration. In some cases the infiltration left very little of the kidney substance. In others there was a more diffuse increase in connective tissue between the tubules.

In this connection it might be mentioned that these focal changes in the renal cortex gave rise to a mistake on our part in the number of cortical kidney abscesses, as reported in our previous communication. We found that 3 instances which we had supposed were acute abscesses proved on microscopic examination to be focal infiltrations with connective tissue and collections of lymphocytes. In a continuation of our work we have several times been struck by the difficulty in differentiating these focal infiltrations from abscesses macroscopically.

In some previous work (5) in which we attempted to produce kidney lesions in the rabbit with colon bacilli isolated from human pyelocystitis cases, we were able to obtain lesions in the

kidney in only about 12 per cent of the animals injected. It was during the course of these experiments, while controlling the urine in a series of animals before injection, that we examined a female rabbit that constantly had a large number of pus cells in the urine. Cultures taken from a catheterized specimen of urine on several occasions showed always a pure culture of a Gram-negative bacillus that had the cultural characteristics of *Bacillus coli communior*.

The organism had the following characteristics: It grew well on all media. There was a profuse yellowish growth on agar. Gelatin was not liquefied. Litmus milk was rendered acid and coagulated; but there was no digestion of the casein. Indol was produced. There was acid and gas formation in dextrose, lactose and saccharose.

As this bacillus formed the basis of this entire series of experiments, we give with some detail the following history of the animal:

February 7, 1917. The first urine examined showed about 150 pus cells to a low power field.⁴

February 10 to February 20. Daily examination revealed a large number of pus cells, single and in groups.

February 20. A catheterized specimen of urine was cultured in litmus lactose agar, plain agar and broth.

February 21. There were innumerable colonies on both plates.

February 23. Specimens were expressed every other day showing albumin and casts in addition to pus cells.

March 3. Another catheterized specimen was cultured; pure culture, same as obtained on February 20.

The animal was chloroformed, as it was getting very much weaker.

Necropsy. Upon opening the peritoneal cavity the abdominal organs all appear practically normal. The bladder is distended with urine. The stomach, gastro-intestinal canal, spleen, liver, gall-bladder, heart and lungs show nothing abnormal. On dissecting free the overlying organs the ureters on both sides are seen to be considerably dilated as far down as the brim of the pelvis. Beyond this point they appear to be of normal diameter. No apparent pathologic constriction in the ureter at the brim of the pelvis visible. The pelvis of both kidneys are smooth and of a reddish brown color. The capsule strips

readily. On section the cortex is of normal thickness, the striations regular. The outer portion of the medulla is deeply congested. The pelves of both kidneys are markedly distended. The left kidney pelvis is filled with a thin purulent material, the right practically empty. The bladder urine show only relatively few leucocytes, numerous casts and much débris. Cultures taken from the bladder and right kidney pelvis yield a pure culture of Gram-negative bacillus.

Histology. The bladder mucous membrane in the entire section is practically intact. In areas there are small clusters of lymphocytes; there are practically no polymorphonuclear leucocytes to be seen in the section. Ureter: A series of 12 blocks taken from the ureter show only a distended lumen without any infiltration, acute or chronic. Kidney: There is considerable degeneration of the epithelium and dilation of the collecting tubules; in areas focally there is considerable increase in connective tissue. In the medulla, especially toward the tip of the papilla, there is marked leucocytic infiltration about the tubules. Eosinophil cells are much in evidence. The mucosa of the pelvis is apparently thickened and shows considerable infiltration with leucocytes (fig. 1). The pelvis is filled with masses of polymorphonuclear leucocytes.

EXPERIMENTAL TECHNIQUE

The technique used in the experiments was as follows: The intravenous injections were made with a bacterial suspension made by centrifuging 15 cc. of a twenty-four hour broth culture and suspending the bacilli in 5 cc. of physiologic sodium chlorid solution. One cubic centimeter of this suspension was injected into the ear vein. The intravesical injections were made after carefully catheterizing the animals and allowing 5 cc. of the bacterial suspension to run into the bladder. In the feeding experiments 8 cc. were introduced into the stomach by means of a tube. In the rectal injections 8 cc. of bacterial suspension were introduced as high as possible through a rectal tube.

In the intravenous series of experiments 31 animals were injected. The first 10 animals received 3 injections at intervals of two days. The remaining 22 received only a single injection of 1 cc. of a twenty-four hour culture of the organism. Of the 31 animals injected, 17 showed a definite pyelitis. This pyelitis

was unilateral in 5 instances and bilateral in 12. In 9 instances there were cortical abscesses in addition and in 1 instance medullary abscesses. Only 1 of the 5 cases in which the pyelitis was unilateral were there any abscesses in the cortex. The lesions in the pelvis usually consisted of a purulent exudate

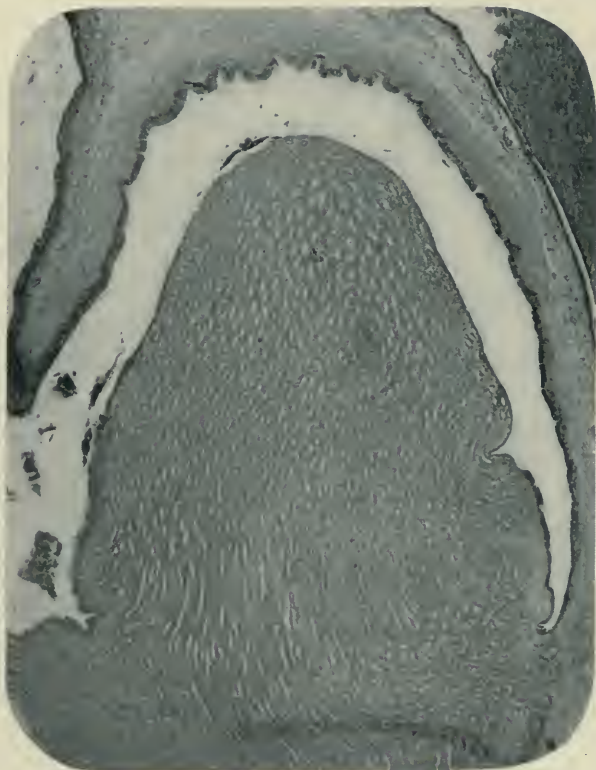


FIG. 1. SECTION THROUGH RABBIT PELVIS SHOWING COLLECTIONS OF LEUCOCYTES AND THE THICKENED MUCOSA

within the lumen and submucous infiltration with pus cells just beneath the mucous lining of the papilla. This submucous infiltration which in the milder cases involved only the papilla but in the more severe types extended also to the parietal lining of the pelvis, was probably the most typical lesion observed

TABLE 1
Intravenous injections

ANIMAL	MICRO-ORGANISMS FROM	DATE OF INJECTION	DATE OF DEATH	KIDNEY			CYSTITIS	URINE		REMARKS
				Pyelitis	Abscess	B. coli		Pus.	B. coli	
R18	R11	February 23	March 23	0	0	0	0	0	0	
R19	R11	February 23	March 29	Unilateral	0	0	0	0	0	Abscess of hind leg
R20	R11	February 23	March 19	0	0	0	0	0	0	Small hemorrhage of cortex
R21	R11	February 23	March 16	0	0	0	0	0	0	
R22	R11	March 8	March 10	0	0	0	0	0	0	
R23	R11	March 7	March 15	0	0	R 0	0	0	0	
R24	R11	March 7	March 29	0	0	L 0	0	0	0	
R25	R11	March 8	March 29	0	0	0	0	0	0	
R26	R11	March 8	March 15	Bilateral.	Medullary	0	0	0	0	
R27	R11	March 8	March 16	Bilateral.	Cortical	0	0	0	0	
R36	R26	March 17	March 21	Bilateral	Cortical	0	0	0	0	
R37	R26	March 17	March 23	Unilateral	0	0	0	0	0	
R40	R27	March 19	March 21	0	0	0	0	0	0	Diphtheritic colitis.
R41	R27	March 19	March 29	Bilateral	0	0	0	0	0	
R42	R27	March 19	March 23	Bilateral	Cortical	0	0	0	0	Broncho-pneumonia
R45	R36	March 22	February 28	0	Cortical	0	0	0	0	
R46	R36	March 22	March 25	Bilateral	Cortical	0	0	0	0	
R60	R42	March 29	April 2	0	0	0	0	0	0	
R61	R42	March 29	March 31	Bilateral	Cortical	0	0	0	0	
R62	R42	March 29	April 3	Bilateral	Cortical	R 0	0	0	0	
R63	R42	March 29	March 31	Unilateral	0	0	0	0	0	
R64	R42	March 29	April 6	Bilateral	Cortical	0	0	0	0	
R75	R41	March 31	April 15	Unilateral	Cortical	0	0	0	0	Abscess in groin—Bac. coli

	R41 R64	March 31 April 9	April 2 May 1	0 Unilateral	Cortical 0	% %	— —	0 %	% %	Chronic nephritis Ureters injected. Bladder culture. Mixed staphylo- coccus and B. coli
R76 R81	R64	April 9	April 16	0	0	0	0	0	0	Bladder culture. Mixed staphylococcus and B. coli. General peritonitis
R82	R64	April 9	April 16	0	0	0	0	0	0	
R83 R84 R89 R90 R91	R47 R47 R41 R41 R41	April 9 April 9 April 22 April 22 April 22	April 12 April 19 April 30 April 30 April 30	Bilateral 0 Bilateral Bilateral 0	Cortical Cortical 0 L Cortical 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	
Total, 31				17	13					

in this group of cases. This was particularly striking in several instances, in which the purulent exudate during the course of examination had been washed out of the pelvis and practically the only lesion to be observed on histological examination was this thin zone of leucocytic infiltration just beneath the mucosa of the papilla. In the more severe cases there was a leucocytic zone of infiltration of considerable thickness below the mucosa. In the less severe cases only scattered polymorphonuclear leucocytes were seen below the mucosa. Pus cells wandering through the mucosa were relatively infrequent.

In those cases in which the pyelitis was complicated by cortical abscesses, the purulent material could usually be traced through the medulla into the pelvis. Whether a large series of section taken through this part of the kidney would have shown miliary abscesses in the cortex or medulla is a question that would be difficult to answer. In a number of animals several blocks were studied and in only one instance were abscesses found that had not been discovered macroscopically. This instance was not included in this series of experiments, because we have not included any animals dying within the first twenty-four hours. The abscess formation was characterized by the collection of pus cells within the glomeruli. In the section studied there was nothing found to suggest that the bacteria were carried directly to the capillaries lining the pelvic wall, rather than that they were excreted through the glomeruli and then carried down with the urine through the pelvis. It is striking as mentioned above that the infiltration of the pelvic wall was always most marked beneath the lining of the papilla. The eosinophilic leucocytes, because of their definite staining qualities, could be recognized in large numbers in these exudates. In order to compare the series of intravenous injections with those of intravesical injections, all the sections of the entire series were gone over once more to study in particular the question of infiltration about the pelvis, especially in its parietal portion, where it joined the ureter. Of the 13 cases of pyelitis there were two instances, animals 42 and 64, showing definite infiltration about the pelvis and extending down toward the

ureter. In animal 81 there was considerable infiltration limited rather strictly to the parietal wall of the pelvis and not extending down toward the ureter. In animal 75 there was considerable parietal infiltration of more chronic nature however. It is thus seen that in only a small proportion of cases was the parietal infiltration of any significance. The majority of the cases in the sections studied showed practically no infiltration.

In none of these experiments was any definite enlargement of the pelvic cavity to be made out. The pelvis, frequently distended with pus, never showed a pyonephrosis as did the original rabbit (R17.11).

The localization of colon bacilli in the kidney was very striking, 20 out of 31 animals showing renal lesions. Of equal importance is the fact that in only four instances were there any definite lesions outside the urinary tract which could be ascribed to the colon bacillus. These lesions consisted of one instance each of abscess of the seminal vesicle, diphtheritic colitis, hemorrhage of the caecum and generalized peritonitis. In our previous series, on the other hand, only 8 out of 66 animals showed kidney lesions and 21 of these 66 showed lesions elsewhere in the body. If the results of these two series of experiments are compared it is evident with what specificity this organism tends to localize in the kidney. In the present series of experiments coccidiosis was exceptional rather than the rule, while in the previous series it was quite prevalent. Whether or not this had anything to do with the localization of the colon bacilli in the other organs it is rather difficult to say.

The following is a detailed study of 4 rabbits from the time of intravenous injection of bacterial suspension to autopsy:

R17.19. Weight 1 pound 4½ ounces

February 23. Urine examined before injection: Microscopically there are no cells or casts; no albumin. Culture of urine shows no organism present in 1 cc. of urine. 1 cc. of thirty-six hour culture of urine of R17.11 was injected intravenously.

February 24. Urine examined. Microscopic examination negative; acid reaction; no albumin present.

February 26. Urine examined. About 10 pus cells to low power field. Temperature 40.7°.

February 27. Urine examined. About 10 pus cells to low power field. No albumin.

February 27, p.m. Reinjected as above with 1 cc. of twenty-four hour culture from urine of R17.11.

February 28. Urine examined. About 10 pus cells to low power field; acid reaction; albumin present.

March 1. Urine examined. Microscopic examination is negative.

March 2. Urine examined. About 10 pus cells to low power field; acid reaction; albumin present.

March 6. Urine examined. About 40 to 50 pus cells in low power field; acid.

March 7. Urine examined. 150 to 200 pus cells, single and in groups, are seen; no casts. The temperature was 39.8°.

March 8. 200 pus cells single and in groups; no casts.

March 9. Urine is loaded with pus cells and casts. Smear shows myriads of Gram-negative bacilli, which is the only organism present.

March 10. Catheterized. Urine loaded with pus cells. Urine plated on plain agar and in broth. Plate is covered with colonies. Broth contains pure culture of Gram-negative bacilli. Plates contain only colonies of Gram-negative bacilli.

March 12. Diarrhea.

March 14. About 100 pus cells to low power field.

March 16. Many pus cells, single and in groups.

March 20. 150 to 200 pus cells in low power field.

March 26. Many pus cells, single and in groups; 5 to 6 granular and hyaline casts; albumin present.

March 29. Died.

Autopsy. Upon opening the peritoneal cavity the bladder contains a small amount of urine in which are found a few pus cells. The kidneys appear normal externally and on section. Both pelves are empty. There is a slight injection of the urethra. Culture of the bladder urine yields a Gram-negative bacillus. The other organs show nothing unusual.

Microscopic examination. Left kidney: There is considerable cloudy swelling of the epithelium of the convoluted tubules. There is a slight excess of eosinophil cells in the glomeruli. The cortex is otherwise negative. The medulla shows nothing unusual. The pelvis contains no exudate and the mucous membrane is not infiltrated with

pus cells. Right kidney: This resembles the left except that there is more marked infiltration of the glomeruli with eosinophil cells. There are no areas of infiltration but the eosinophil cells are scattered quite diffusely throughout the cortex. The medulla shows nothing unusual. The pelvis contains a purulent exudate consisting largely of polymorphonuclear leucocytes and some detritus. The mucous membrane throughout almost its entire extent is infiltrated with leucocytes,



FIG. 2. PUS IN LUMEN; LEUCOCYTES IN TISSUE

many of them of the eosinophil type. The bladder shows nothing abnormal. The ureter shows slight desquamation of the epithelium in the lumen. There are no pus cells and no periureteral infiltration. The urethra shows nothing abnormal.

R17.27. Weight, 2 pounds 6 ounces

March 8. Urine: Microscopic examination negative; faintly alkaline; albumin absent. Injected intravenously with $1\frac{1}{4}$ cc. of a suspension

in 4 cc. of salt solution of 15 cc broth culture of *B. coli* from right pelvis of R17.11.

March 9. Urine: Microscopic examination negative.

March 10. Urine is loaded with pus cells.

March 12. Urine is loaded with pus cells. Trace of albumin is present.

March 14 to March 16. Many pus cells in urine.

Sacrificed.

Autopsy. Upon opening the peritoneal cavity the bladder vessels are distended and the tissues about the bladder somewhat edematous. The bladder is empty. The liver and gastro-intestinal canal are negative. The kidneys are of a dark brown red color and scattered irregularly throughout the surface are numerous opaque yellow areas varying in diameter from 1 to 3 mm. The ureters are definitely injected on the serous surface. From the cut section of both ureters pus can be expressed. Upon section of the kidney the cortex looks practically normal. Extending down from the cortex almost to the papillae are numerous yellow lines, widest at the cortex and narrowing toward the papillae. The pelves appear smooth, slightly injected. The right kidney pelvis contains pus. The lungs and heart show nothing unusual. The bladder shows numerous small hemorrhages on the surface. Cultures from the abscesses of the right and left kidney all show Gram-negative bacilli.

Microscopic examination. The bladder in the section studied shows practically an intact mucous membrane which in most areas is definitely infiltrated with polymorphonuclear cells. In some areas, just beneath the mucosa are seen small hemorrhages. In some areas in the same location there are collections of large number of leucocytes. The left kidney cortex shows considerable degeneration of the epithelium. In certain areas there is marked infiltration with polymorphonuclear leucocytes, distending the tubules and with considerable infiltration about them. In other areas the structure of the kidney is entirely lost and is just one large mass of leucocytes. This same holds true of areas in the medulla, extending down toward the papilla. The medulla is otherwise negative. The pelvis is filled with a purulent exudate. The lining of the pelvis does not show very much infiltration with leucocytes in the section studied. Section through the right kidney shows no abscesses in the cortex and only small areas of infiltration into the medulla. The pelvis is empty and there is no infiltration of the epithelium of the pelvis. The ureter shows nothing abnormal.

R17.36

March 17. Urine: Microscopic examination negative; albumin absent; faintly alkaline. Injected intravenously with 1 cc. of a suspension in 5 cc. of salt solution of 15 cc. of a broth culture (forty-eight hours) of *B. coli* from the pelvis of the right kidney of R17.26.

March 19. Urine shows about 20 pus cells in low power field.

March 20. Urine shows many pus cells, single and in groups; albumin absent; acid reaction.

March 21. Urine loaded with pus cells.

Died.

Autopsy done immediately after death. The bladder is distended with urine loaded with pus cells. The ureters are distended, especially so near the pelvis. Pus is expelled from the cut end of both ureters. Right kidney: Externally there are seen many small abscesses on the surface. On longitudinal section pus exudes from the pelvis. The kidney otherwise appears normal. Left kidney: There are a few abscesses on the surface which is otherwise smooth. On section pus exudes from the pelvis. The spermatic sac is somewhat injected and contains some pus. The gastro-intestinal canal is entirely normal. There is coccidiosis of the liver and gall bladder and also of the heart. The lungs show slight congestion. Cultures of the bladder, right and left kidney pelvis all show Gram negative-bacilli.

Microscopic examination. The lungs show marked congestion and in some small areas an inflammatory exudate. The bladder shows nothing abnormal. The kidney cortex shows marked swelling of the epithelium but no excess of cells in the glomeruli. In one area there is a purulent infiltration of several glomeruli and tubules extending down into the medulla. This infiltration disappears in the medulla in the section studied. The very tip of the papilla shows immediately underneath the mucous membrane a wide zone of infiltration with leucocytes. This zone gradually shades off into a single layer of cells underneath the lining of the pelvis. The pelvic mucosa shows considerable infiltration with polymorphonuclear leucocytes. The pelvis contains a small amount of pus. In one area there is a hemorrhage just beneath the pelvic mucosa. The lining of the upper portion of the ureter shows no infiltration nor is there any periureteral infiltration.

R17.81

April 9. Urine: Microscopic examination negative; albumin absent; acid reaction. Injected intravenously with 1 cc. of a suspension

in 3 cc. salt solution of 10 cc. broth culture of the organism from R17.64.

April 13. Urine: Microscopic examination negative.

April 16. Urine shows 30 to 40 pus cells and several casts.

April 19. Urine: Microscopic examination negative.

April 23. Urine: Microscopic examination negative.

April 25. Urine shows granular casts and many pus cells in clumps.

April 28. Urine shows 10 to 15 granular casts and a few small groups of pus cells.

May 1. Died.

Autopsy. The bladder urine contains casts and epithelial cells but no pus cells. The right kidney appears normal externally and on section. There is no pus in the pelvis of the right kidney. The left kidney resembles the right externally. On section there is a considerable amount of pus in the left pelvis. The stomach and intestinal canal are entirely normal. There is some coccidiosis of the gall bladder and liver. The autopsy is otherwise negative. Cultures from the bladder urine contain Gram-positive cocci and Gram-negative bacilli. Culture from the left kidney pelvis shows only Gram-negative bacilli.

Microscopic examination. Left kidney: The cortex shows inflammatory infiltration. The glomeruli appear normal and the medulla shows no definite areas of acute infiltration. The pelvis contains considerable amount of purulent exudate but only slight infiltration of the wall over the papillae. The submucous infiltration is more marked in the parietal portion of the pelvis. The right kidney shows a normal cortex and medulla. There is no pus in the pelvis and no evidence of infiltration of the wall.

INTRAVESICAL INJECTIONS

A total of 15 animals received intravesical injections of from 5 to 8 cc. of a broth culture of *Bacillus coli communior*. At the time of the injection the bladder was first drained of its urine and this urine was cultured in each instance. In no instance was there a Gram-negative bacillus found and in none were there more than a few organisms per cubic centimeter of urine. The broth culture was allowed to run into the bladder by gravity. In order to make sure that by this procedure no material reached the ureters, we injected 3 animals with gentian violet in the

TABLE 2
Intravesical injections

ANIMAL	MICRO-ORGANISMS FROM	DATE OF INJECTION	DATE OF DEATH	KIDNEY			CYS-ITIS	URINE		REMARKS
				Pyelitis	Abscess	B. coli		Pus	B. coli	
R31	R26	March 17	April 17	0	0	0	##	##	##	Heart culture negative Heart culture negative
R32	R26	March 17	April 9	0	0	0	##	##	##	
R47	R36	March 22	April 6	Bilateral	0	##	##	##	##	
R49	R36	March 22	March 31	Bilateral	0	##	0	##	##	
R50	R42	March 29	April 11	0	0	L#	##	##	##	Pus in pelves, ureters dis- tended Entirely normal kidney ma- croscopically
R51	R42	March 29	April 11	Bilateral	0	R0	##	##	##	
R52	R42	March 29	April 11	Bilateral	0	L0	##	##	##	
R53	R42	March 29	April 11	0	0	R#	##	##	##	
R54	R42	March 29	April 11	0	0	L#	##	##	##	Bladder culture. Mixed B. coli and staphylococcus
R56	R41	March 31	April 11	Bilateral	0	R#	##	##	##	
R68	R41	March 31	May 4	Unilateral	0	R#	0	##	##	
R77	R64	April 9	May 5	Bilateral	0	L0	—	##	##	
R78	R64	April 9	April 16	Bilateral	0	—	##	##	##	Pus in vagina
R85	R47	April 9	April 21	Bilateral	0	R#	0	##	##	
R86	R47	April 9	May 9	Unilateral	0	L#	0	##	##	
Total, 15				10	1	2				

same manner. In none of them were we able to find the bladder markedly distended or any evidences that the fluid had passed into the ureters. Since these experiments we have used this same technic with another series of rabbits and found much to our disappointment that the infection was limited to the bladder in the great majority of instances.

Of this first series of 15 animals, 10 developed pyelitis, 8 bilateral and 2 unilateral. In one of the instances of unilateral pyelitis the culture from both kidneys was positive but evidence of inflammation was present in only one kidney. In one case only, R66, were there cortical abscesses. These abscesses were present in a small group in only one area of each kidney. They differed in this respect from the abscesses following intravenous injection which were always diffusely scattered over the surface. Furthermore they were surrounded by quite a wide zone of hemorrhagic infiltration.

In two instances, R49 and R54, there were no findings either macroscopic or microscopic but we were able to cultivate the *Bacillus coli communior* from the kidney pelvis. All cultures taken from the heart's blood at autopsy were found to be sterile.

If we compare the pathology of the intravesical injections with that of the intravenous injections, we find that the parietal infiltration is much more evident in the former. Although some of the intravesical injections caused infiltration of the mucous membrane of the papilla, it is found only in those cases in which the infiltration of the parietal membrane is very marked. In some instances there is parietal infiltration but absence of any submucous infiltration of the papilla. In rabbit 52 there is definite parietal infiltration with slight infiltration of the papilla. Animal 66 of all this series probably best shows the course of the infection. The bladder shows very marked infiltration of the wall. The section of the ureter entering the bladder shows a definite polymorphonuclear infiltration, both in the muscle layers as well as in the periureteral tissue. Near the uretero-pelvic junction, the ureteral wall is densely infiltrated with an acute exudate and the parietal portion of the pelvic mucosa is densely infiltrated with cells. The abscesses, as men-

tioned above, were limited in each kidney to a small portion of the cortex and the direct connection between the abscesses and the pus-filled tubules down to the pelvic cavity could be demonstrated. The sections of the bladder, ureter and kidney (figs. 2 and 3) especially when these are compared with sections of the same organs from animals receiving intravenous injections, readily show the course of the infection and this can be traced from the bladder to the cortex of the kidney. From this severest type of ascending infection, we have all transitions to the type in which we were able to find only the colon bacillus in culture from the pelvis of the kidney without any lesions, macroscopically or microscopically. At this point we do not wish to go more particularly into the question of the ascending infection, except to say that it seems to us that these experiments, by the mode of injection and by the pathological condition found, prove quite definitely that the infection traveled up the periureteral lymphatics to the kidney, rather than that from a primary cystitis a secondary infection of the kidney occurred by way of the blood stream. We hope at a later date to go more minutely into the histological findings in cases of ascending infection. Further experiments in this connection are at present under way.

The following is a detailed study of 4 rabbits receiving intravesical injections of bacterial suspensions.

R17.54

March 29. Urine: Microscopic examination negative; albumin absent; acid reaction. Catheterized specimen of urine was plated; no growth. 5 cc. broth forty-eight hour culture from the pelvis of the left kidney and bladder of R17.42 were injected intravesically.

March 30. Urine shows 8 to 10 pus cells.

April 2. Urine shows many pus cells and 6 to 8 granular and hyaline casts.

April 4. Urine shows 20 to 30 single cells and several groups.

April 10. Urine loaded with pus cells and several casts.

April 11. Sacrificed.

Autopsy. The bladder is somewhat edematous and is filled with urine containing many pus cells mostly in troups. The ureters and kidneys show nothing abnormal, externally or on section. Cultures

from the heart and the right kidney are negative; from bladder and left kidney positive for Gram-negative bacilli.

Microscopic examination. The bladder: The epithelium is markedly infiltrated with pus cells. The subepithelial layer and also deeper layers of the bladder show considerable polymorphonuclear infiltration. Right kidney: The cortex and medulla show no evidence of infiltration. The pelvis is empty and the mucosa shows no infiltration. Section

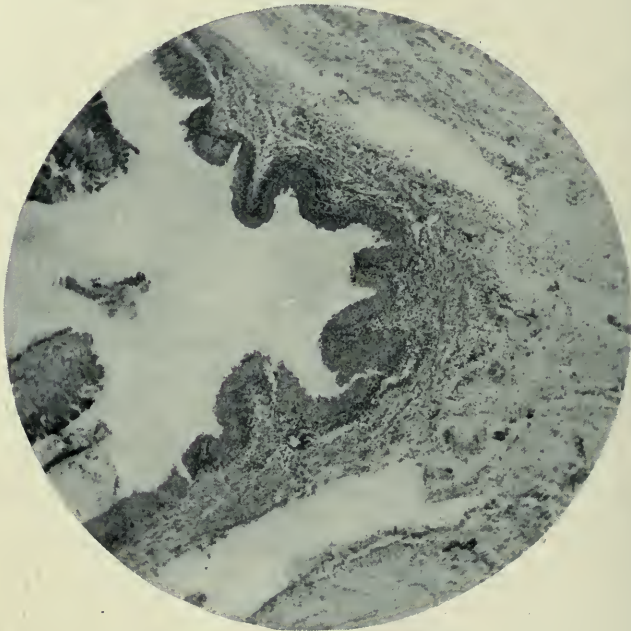


FIG. 3. PYELITIS; PERI-PELVIC INFLAMMATION

of the ureter shows nothing abnormal. Left kidney: The cortex and medulla show nothing abnormal. There is no exudate in the pelvis. The epithelium of the pelvis shows no infiltration at any point. The section of the ureter shows an empty lumen and no infiltration of the mucosa or of the periureteral tissues.

R17.66

March 31. Urine: Microscopic examination shows some epithelial cells; acid reaction; albumin absent. Catheterized specimen plated: One colony on plate—*staphylococcus albus*.

March 31. 6.cc. broth twenty-four hour culture of organisms from R17.41 were injected intravesically.

April 2. Urine shows many pus cells, single and in groups.

April 4. Urine is loaded with pus cells, single and in groups; no casts.

April 10. Urine loaded with pus cells and casts. Animal in poor condition.

April 11. Sacrificed.

Autopsy. Upon opening the peritoneum the bladder contains a small amount of urine filled with pus cells and casts. The bladder wall appears slightly edematous. The kidneys externally show a group of small hemorrhagic lesions with yellowish centers. On section these lesions are seen to extend through the cortex down into the medulla. There too they appear rather hemorrhagic (see figure 3). The pelves are distended with pus. Cultures from the bladder and right kidney show pure culture Gram-negative bacilli. Culture of the heart's blood is negative.

Microscopic examination. Right kidney: Sections taken from three serial blocks.

Block I. For the most part the kidney cortex appears entirely normal. In one area, however, there are numerous small infiltrations of polymorphonuclear leucocytes near the glomeruli and surrounding tubules. In the central one of these areas the process has spread breaking through the tubules and showing quite a wide zone of infiltration. Extending from this area there are several streaks running down into the medulla and on cross section small groups of tubules in the medulla are seen filled with a purulent exudate, the walls of which show considerable polymorphonuclear infiltration. The pelvis contains pus. The walls in some areas show polymorphonuclear infiltration which, however, is not very marked.

Block II. In the section from this block the cortex appears entirely normal with the exception of infiltration in one glomerulus. The upper portion of the medulla also appears perfectly normal and no streaks are seen running down. In the lower portion of the medulla cut in transverse section are seen numerous groups of tubules densely filled with purulent exudate. Many of them are surrounded by a collar of infiltration. In this section the pelvis contains pus and shows very much more marked infiltration of the pelvic mucosa.

Block III. This runs through the tip of the papilla and shows a large opening of the tubules filled with a purulent exudate and showing

in numerous places dense infiltration in the peritubular tissue. The epithelium on the side of the papilla seems to be thickened and on sections shows small groups of pus cells surrounded completely by epithelium. The mucosa of the pelvis shows some infiltration, but the subepithelial infiltration is much more marked. The cortex in this section shows nothing abnormal. The loose areolar tissue about the pelvis shows a large excess of polymorphonuclear cells. The vessels show nothing unusual.

R17.68

March 31. Urine: Microscopic examination negative; albumin absent; alkaline reaction. Catheterized specimen plated: one colony staphylococcus albus in 1 cc. of urine. Six cubic centimeters of a twenty-four hour broth culture of organisms from R17.41 were injected into the bladder.

April 2. Urine shows many pus cells, single and in groups.

April 4. Urine shows 50 to 60 pus cells in low power field but no casts.

April 10. Urine shows 4 to 5 pus cells but no casts and no débris.

April 13. Urine shows 40 to 50 pus cells.

April 16. Urine loaded with pus cells.

April 19. Urine shows strings of pus but few in the remainder of the urine.

April 23. Impossible to obtain specimen.

April 25. Urine loaded with pus cells and strings of pus, also 8 to 10 granular casts; albumin present.

April 28. Urine shows 18 to 20 granular and hyaline casts and many pus cells, also some strings of pus.

May 2. Urine loaded with pus cells and casts.

May 4. Dead.

Autopsy. Upon opening the peritoneal cavity the bladder urine contains many pus cells and casts. The bladder is normal. The vagina contains a small amount of pus. The ureters are somewhat injected, particularly the right. The kidneys appear normal externally and on section, except for pus in the pelvis of the right. The left pelvis was empty. The other organs are entirely negative. The bladder and right kidney pelvis yield in culture only Gram-negative bacilli. The culture from the left kidney pelvis was negative.

Microscopic examination. The right kidney shows a normal cortex except in one area there is some lymphoid infiltration about the ves-

sels extending down between several of the tubules. In the medulla there are several areas where there is infiltration with lymphocytes. Near the tip of the papilla several tubules are filled with an exudate containing polymorphonuclear cells. The pelvis is practically empty. The pelvic mucosa shows in some areas slight submucous infiltration. Left kidney: This shows no changes in the cortex, medulla, or pelvis.

R17.86

April 9. Urine: Microscopic examination negative; albumin absent; acid reaction. Five cubic centimeters of a broth culture of R17.47 were injected intravenously. Catheterized specimen of urine plated.

April 11. First specimen plated; shows 3 colonies of Gram-positive coccus.

April 13. Urine loaded with casts; granular.

April 15. Urine loaded with pus cells, and 20 to 50 granular casts.

April 19. Urine shows 10 to 12 pus cells.

April 23. Urine shows many pus cells and 5 to 6 granular casts.

April 28. Urine shows 20 to 30 pus cells and 2 to 3 granular casts, also much debris.

May 2. Urine loaded with pus cells and contains many casts. Urethra swollen and apparently infected.

May 9. Animal died.

Autopsy done immediately. The bladder is distended with urine which contains many pus cells and casts. The ureters and bladder are normal externally. Both kidneys appear normal externally. The left pelvis contains pus on section. The right pelvis contains none. There is some pus in the vagina. The autopsy is otherwise negative. Culture from both kidneys and bladder yield pure culture Gram-negative bacilli.

Microscopic examination. The right kidney cortex and medulla show no evidence of any acute inflammatory infiltration. There are few collections of mononuclear cells in the cortex. The pelvis is empty and there is no apparent infiltration of the wall of the pelvis. The left kidney also shows an area of lymphoid infiltration in the cortex. The medulla is negative. There is a purulent exudate in the pelvis but practically no infiltration of the pelvic mucosa. The ureters show nothing abnormal.

TABLE 3

ANIMAL	MICRO-ORGANISMS FROM	DATE OF INJECTION	DATE OF DEATH	KIDNEY			CYS-TITIS	URINE		REMARKS
				Pyelitis	Abscess	B. coli		Pus	B. coli	
Oral injections										
R55	R42	March 29 March 31 April 3	April 22	0	0	R#	0	0	%	Autopsy several hours after death
R56	R42	March 29 March 31	April 3	0	0	0	0	0	0	Urine contains casts
R57	R42	March 29 March 31 April 3	April 27	0	0	0	0	0	%	Mixed bladder culture. B. coli and Gram-positive cocci. Granular and hyaline casts in urine
R58	R42	April 3	May 8	0	0	0	0	0	0	Casts in urine, no pus
R59	R42	April 3	April 4	0	0	0	0	0	0	
R69	R41	March 31 April 5	April 26	0	0	0	0	0	0	
R70	R41	April 5	April 16	0	0	R0	0	0	0	
R71	R41	April 5	April 5	0	0	0	0	0	%	
R72	R41	April 5	April 7	0	0	0	0	0	0	
Rectal injections										
R79	R64	April 10	April 30	0	0		0			Casts in urine
R80	R64	April 10	April 16	0	0	0	0	0	0	Casts in urine
R87	R47	April 10	April 27	0	0		0	0	%	Injection of intestines
R88	R47	April 10	April 21	0	0		0			

0 = absent

* = present

ORAL INFECTIONS

As a control, we fed 9 animals with the strain of *Bacillus coli* communior which we employed in these experiments. Most of the animals received 8 cc. of the culture on three occasions. A number of the animals showed a marked degree of diarrhea but in no instance did any infection develop in the urinary tract. In one instance in which the autopsy was done some hours after death, a colon bacillus was isolated from the kidney and bladder. In two other cases in which the autopsy was done shortly after death, the *Bacillus coli* was obtained from the bladder urine. Eight of the nine animals apparently died from the results of the feeding but the urinary tract was free from any involvement.

R17.56

March 29. Urine contains a few epithelial cells; no albumin and acid reaction. Fed 5 cc. forty-eight hour broth culture from the pelvis of the left kidney and bladder of R17.42.

March 30 and March 31. Urine: Microscopic examination is negative.

March 31. Fed 8 cc. forty-eight hour broth of R17.42.

April 2. Urine shows a large number of granular casts, about 20 to 30. No pus cells.

April 3. Dragging left hind leg and so sacrificed.

Autopsy. The bladder is markedly distended with urine containing a large number of casts but no pus cells. The other organs are entirely negative. In the muscles of the right thigh are numerous and extensive hemorrhages. Cultures of the muscle, the bladder urine and the pelvis of the right and the left kidneys are negative.

Microscopic examination. The cortex of both kidneys shows nothing abnormal. The medulla contains numerous epithelial casts in the collecting tubules. The pelvis are empty and the pelvic lining shows nothing abnormal.

R17.79

April 9. Urine: Microscopic examination negative; albumin absent acid reaction.

April 10. Injected the rectum with 8 cc. of a twenty-four hour broth culture of organisms from R17.64.

April 13. Urine: Examination is negative.

April 16. Urine loaded with casts and 20 to 30 pus cells.

April 19. Urine shows 20 granular casts but no pus cells.

April 23. Urine: Microscopic examination is negative.

April 25. Urine shows 30 to 40 casts and 10 to 15 pus cells.

April 28. Urine: Microscopic examination is negative.

April 30. Found dead.

Autopsy. Upon opening the peritoneal cavity the bladder is distended with urine which contains no pus cells or casts. The kidneys and ureters are negative. The other organs appear entirely normal.

Microscopic examination. The cortex, medulla and pelvis of both kidneys are entirely normal.

RECTAL INJECTIONS

In order to determine the effect of rectal injection of this same organism, we injected 4 animals with 8 cc. of broth culture. Several of the animals showed considerable congestion of the lower portion of the intestinal canal. The kidney and bladder findings were entirely negative however. All 4 of these animals died, apparently as a result of the injections.

SUMMARY

Pyelitis has been experimentally produced in the rabbit by the intravenous injection and by the intravesical injection of:

Bacillus coli communior isolated from spontaneous pyelitis in the rabbit.

Pyelitis was produced in 17 of 31 rabbits injected into the ear vein. Ten per cent of the rabbits had also abscesses in the kidney. Three rabbits had abscesses without a pyelitis.

Pyelitis was produced in 10 out of 15 rabbits by intravesical injection. In only one instance were there abscesses in the kidney.

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BEAN-SHAPED DOUBLE KIDNEY—A RARE TYPE OF DYSTOPIA AND FUSION

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Congenital malformations and ectopias of the kidney have so long held the attention and interest of the anatomist and clinician that a very extensive literature of these anomalies has been collected. The horseshoe kidney (*Ren unguiformis*) has been described by many early observers and is the commonest fusion product of the kidneys, having been found to occur in one out of every 715 autopsies in a series of 51,500 protocols (Botez). The sigmoid kidney (*Ren sigmoideus*) first described by Broesike in 1884 has since been reported many times, the case of Winternitz being an excellent example of this type. In addition to these there is a large class of anomalies produced by the more or less complete fusion of the two organs with the formation of lump kidneys (*Ren informis*) and shield kidneys (*Ren scutaneus*), of many bizarre forms and atypical vascularizations, no two of which are identical. In contrast to these irregularly formed kidney masses, there is a type of ectopic fused kidney which possesses all the symmetry of the single organ, save that it has two sets of excretory ducts and functions as two distinct kidneys. That this type of dystopia is very rare is certain, and in spite of a fairly comprehensive review of the literature, we have been able to find but one definite case thus far reported (Huntington). We are prompted therefore to describe another such case, striking in its similarity to the one just referred to, as an interesting study in fetal mal-development.

The kidney was found in the body of a negro aged forty-two years, the cause of whose death was chronic diffuse nephritis with cardiac decompensation. The blood Wassermann was

positive. Except for a greatly dilated heart and left fibrous orchitis, there were no gross structural abnormalities other than those grouped about the kidney mass itself. Examination of the retroperitoneal contents revealed what seemed to be a single large kidney very slightly lobulated lying in its fossa on the right of the vertebral column and projecting prominently into the abdominal cavity. There was no rudiment of renal tissue anywhere else in the abdomen. The long axis of the organ had a normal relation to neighboring structures. With the body in the decubitus position, the organ extended from the 11th thoracic vertebra to a point 1.5 cm. above the iliac crest, a length of 15 cm. The maximum width was 9 cm. The pylorus lay approximately at the hilum with the duodenum covering the medial border of the lower pole. The cavity on the left usually occupied by that kidney contained the splenic flexure of the transverse colon, as well as the sigmoid, which was not pelvic in position. The sigmoid mesocolon was unusually long and originated from a point in the abdomen much higher than normal. The right suprarenal capped the upper pole of the kidney with its usual position and shape. The left suprarenal occupied a somewhat lower position on the opposite side. It was curiously flattened dorso-ventrally and lay beneath the pancreas and adjacent lymph-nodes. While the marked symmetry of the kidney mass led promptly to the conclusion that this was a congenital single kidney—a condition not extremely rare in the literature—examination of its ureteral connections showed that it belonged to an entirely different group of anomalies. The kidney drawn in situ is seen to have two ureters emerging from a single large hilum, the upper of which passes almost vertically downward, crossing the right iliac vessels on its course into the pelvis. The other ureter emerges from the lower part of the hilum, passes obliquely beneath the other duct, crosses the right iliac artery 4 cm. below its bifurcation and the iliac vein 1 cm. below its junction, and thence across the vertebral column into the bladder. The latter presented a normal trigone with the upper and lower ureters entering at the right and left orifices respectively. The seminal vesicles and

vasa deferentia were normal. The kidney from these facts is obviously a congenitally fused double organ but is characterized by the cyamoid or bean-like shape which belongs to the normal kidney. To follow the nomenclature in use, it might thus be termed *Ren cyamoideus duplex*—or bean-shaped double kidney.

Associated with this is another anomaly involving the blood vascular system. As depicted, there is a reduplication of the postrenal segment of the inferior vena cava. The large iliac venous trunks anastomose by a very wide, short channel 4 cm. in diameter at a point opposite the iliac crest and immediately thereupon separate into two large vessels which loop the abdominal aorta in their ascent and reunite ventral to that artery and to its right, approximately 1 cm. below the caudate lobe of the liver. It passes on through its notch in the liver to the heart as a single large vessel. These two postrenal segments of the vena cava are practically equal in section. The right segment occupies the position of the normal postcaval vein. The left is slightly longer and crosses the aorta obliquely between the two mesenteric arteries before its junction with its mate on the right. The inside length of the ellipse thus formed is 7.5 cm. The renal veins are three in number, two of which make their exit from the hilum and join the vena cava at its upper anastomosis. The third is a small aberrant vessel which leaves the renal parenchyma directly and with a slight descent joins the caval trunk at the lower anastomosis. The reduplication of the vena cava and the absence of a kidney to the left of the body axis necessarily changes the relations of the testicular veins. On the right this vein breaks up into two vessels just below the iliac crest, one of which enters the middle renal vein and the other the right postcaval vein close to its junction with the left. The left testicular vein is single and joins the left caval segment about halfway between the upper and lower anastomoses.

Aside from the aberrant artery which enters the parenchyma with the vein at the lower pole of the kidney, the arterial supply is essentially normal. Besides this smaller artery there is a main vessel which enters the hilum and divides into several branches before entering the renal tissue. The spermatic arteries are given off from the aorta in the usual manner.

Consideration of the disposition of the pelves and the blood vessels within the kidney seemed advisable, and the corrosion method being impossible, because of a previous mass injection, dissection was attempted. The drawing shows excellently the

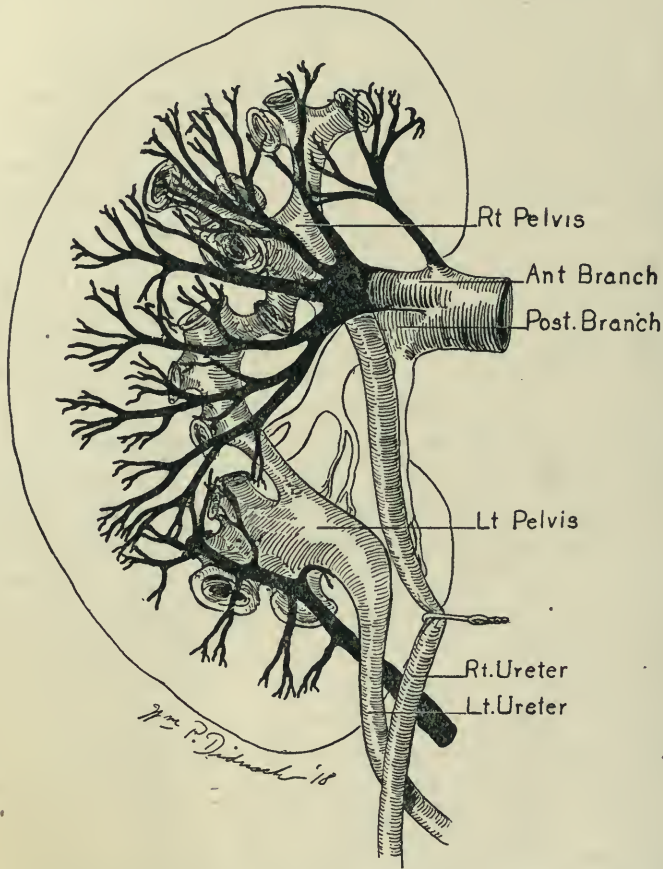


FIG. 1. DIAGRAMMATIC SKETCH SHOWING ARTERIAL BLOOD SUPPLY, RENAL PELVES AND URETERS

relation of pelves and arteries. Dissection confirmed the impression that the kidney was a unit mass; the large single hilum opened into a single sinus renalis in which the pelves bifurcated to their respective points of distribution. A slight overlapping

of the adjacent calyces of the two pelves completes the fusion picture. Notwithstanding, the kidney clearly functioned as a double organ—the right pelvis serving the upper half and the left the lower half of the mass. The intrarenal arterial supply follows essentially the normal plan of vascularization pointed out by Brödel. The main large artery divides into anterior and posterior branches between which lies the pelvic portion of the ureters. The single aberrant artery has a purely local distribution on the anterior aspect of the lower third of the organ.

The permanent kidney begins as an outbudding from the Wolffian duct near its entrance into the cloaca. Growing cranialward, this renal bud becomes intimately associated with a mass of mesenchyme within whose substance it bifurcates many times forming the ureter, pelvis, and collecting tubules. The mesenchyme itself becomes the renal parenchyma proper. The ureter and hilum of the pelvic kidney are ventral rather than medial to the renal mass and it is not until its migration to its permanent position in the abdomen is completed that its rotation medialward takes place. This migration occurs between the fifth and seventh weeks and marks the period of renal fusion. As pointed out by Lewis and Papez and others, one of the chief factors in renal fusion is the ring formed by the umbilical arteries (common iliaes) at the pelvic rim. As the kidneys progress through this constricted vascular ring toward the abdomen they are brought together, first the upper poles, then the bodies of the organs and finally the lower poles as they pass into the abdominal cavity. Since the kidney is larger as it completes its passage through the ring than earlier in its ascent, fusion is most likely to occur at this time with the production of the typical horseshoe kidney. Again as Pohlman suggests, if one kidney is in advance of the other in its migration, fusion may take place variously to form the sigmoid and other types of anomaly. In each case, due to the asymmetry of the resulting mass, medial rotation is arrested and the hilum remains ventrally placed.

The present case belongs apparently to this latter group. For some reason the right renal bud started its migration earlier or

more rapidly than did the left. When fusion took place, it was practically end to end but with the lower pole of the right somewhat overlapping the upper pole of the left. The cephalic kidney (the right) then took the lead as is usually the case (McMurrich), drawing the caudal kidney to its own side. It is irrelevant and hopeless to speculate on the factors brought to bear on this renal mass to mold it from an elongated fused organ into the normal cyamoid shape. The circumstances were unusual for the elongated fused kidney in adults is not the most uncommon anomaly, whereas the present case is almost unique. It is obvious, however, that this must have taken place before it reached its final position in the abdomen, otherwise the permanent blood vessels which it receives at that time would have materially hindered any further change of shape. Rotation seems to be largely a matter of the formed kidney adjusting itself to a pocket in the posterior abdomen (Kelly and Burnam). If asymmetrical, the kidney does not easily fit into this renal pocket and rotation is prevented, the ureters remaining ventral. While this latter condition usually obtains, in this case rotation took place; hence the molding process was apparently completed before the usual rotation period (fifth to eighth weeks). In rotating from a ventral to a mesial position, the right or upper ureter is carried across ventral to the left or lower duct and presents the relations seen in the adult.

Atypical vascularization of the fused kidney is the rule. The typical fused renal mass is pierced by several arteries which are given off from the aorta or iliacs at points conveniently near those portions directly supplied. Even in the normal kidney of unusual length or with divided pelvis, a polar artery is often found assisting the main renal vessel (Kelly and Burnam). Jeidell explains this on the ground that the migrating kidney progressively adopts new vascular relations by capillary anastomoses with the vessels of the Wolffian body and aorta until its ascent is completed. Then one of these aortic anastomoses (usually the twenty-first aortic segment) is retained with atrophy of the others. If, however, the ascent is not completed or if the organ is longer than normal, other anastomotic relations are maintained. The present case is thus easily accounted for.

The reduplication of the postrenal vena cava warrants brief consideration. Persistence of the left postcardinal segment is not an extremely rare condition, Givens and others having collected a number of cases from the literature. It is significant that almost all caval reduplications are postrenal, i.e., inferior to the renal vessels—and the study of the fetal abdominal venous system offers explanation of this. The chief early vessels of the trunk are the paired cardinal veins passing from the cauda up to the large sinuses near the primitive heart. With the development of these comes the appearance of two parallel veins, medial to the cardinals, having vascular relations with the Wolffian bodies and likewise entering the great cardiac sinuses. Of these two subcardinal veins, the right greatly increases in size to form the unpaired prerenal caval segment, and by anastomoses with the two cardinal veins divides the latter into anterior and posterior parts. While the anterior divisions develop into the azygos vessels, the posterior through their anastomoses with the right subcardinal vein, become the lower segments of the early postcaval system. The postcardinal vessels then form a venous ring by a more caudal anastomosis near the pelvic rim (the junction of the iliacs). Normally we should see in the last stage the right postcardinal segment much increased in size as the postrenal vena cava, the left remaining as the slender spermatic vein, except at its proximal anastomosis where it becomes the permanent vein of the left kidney. In the present case, however, this final stage in development is not attained and instead the caudal anastomosis remains; the left postcardinal segment assumes a size and function equal to its mate, receiving rather than becoming the left spermatic vein, which like the right spermatic is formed from one of the early venous channels between the gonad and the postcardinal vessels.

The case reported by Professor Huntington has a remarkable similarity to the present case not only in respect to the kidney itself but also because of the postcardinal reduplication. In Huntington's case, the presacral anastomotic branch between the two caval vessels is a relatively long vein of smaller caliber than the vessels it unites. This fact suggested the probability

that the persistence of the two postcardinals was due to the inadequacy of this anastomotic vessel in conducting blood from the lower limb to the vena cava; hence each cardinal vein was indispensable in receiving blood from the limb on its own side. In the case at hand, however, the very wide and short anastomosis obviously excludes such an explanation. A difference between the two lies also in the ureteral relations; for while in Huntington's case, the right ureter does not cross the other in its descent, it occupies an unusual position dorsal to the right caval segment and iliac vein. These differences, however small in the gross, would, according to Huntington's analysis, indicate distinctly different lines of development. Hence the apparent similarity of the adult structures is probably a remarkable coincidence in which varying factors, brought to bear variously in the two cases, have produced but slightly different end-results.

While the clinical history of the present case was one of chronic diffuse nephritis, review of those cases of anomalous kidneys in which the cause of death was reported offers no evidence of a nephritic diathesis due to the congenital condition, unless of course the abnormality be of the nature of a polycystic kidney. A series of 124 renal anomalies of all types collected by Dorland, in 64 of which the cause of death was stated, showed but one frank case of chronic nephritis occurring in a fused kidney (Poynder). In the other cases where death followed uremia, single or rudimentary organs were generally found.

While there seems to be no special predisposition to chronic renal disease among individuals with congenitally fused kidneys, hydronephrosis and similar surgical conditions are much more common in mal-developed than in normal kidneys. Girard found among 44 cases of renal ectopia 21 cases of hydronephrosis and Papin and Christian, Eisendrath, Braasch, Young and Davis and others have made similar observations. The obstruction responsible for these lesions is caused sometimes by anomalous arteries pressing upon the ureter (Guiteras) or by ureteral kinks, conditions often attending renal ectopia. With this there has been the added danger of possible non-recognition of the fused nature of the renal mass at operation, as in Dennis's case, in

which pan-nephrectomy was done. With the advent of pyelography, however, both congenital renal anomalies and the surgical conditions attending them are now readily recognized.

I wish to acknowledge my indebtedness to Mr. W. P. Didusch, artist to the Brady Urological Clinic, for his courtesy in making the excellent illustrations.

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PLATE 1

Plate showing kidney in situ and relationship to surrounding structures.



CHART FOR RECORDING CYSTOSCOPIC EXAMINATIONS

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The aid of the cystoscope is not needed for the rough diagnosis of prostatic enlargement or malignancy and many surgeons counsel against its use in those cases in which the diagnosis is reasonably sure but there is no question of its advantages when used with care and discretion. It forms the basis of an accurate differential diagnosis of conditions other than prostatism, as well as the types of prostatism itself. It recognizes vesical complications. It gives a better selection of cases for suprapubic or perineal attack. It insures operative thoroughness. Text books of urology and monographs of cystoscopy unanimously advocate the use of the cystoscope in cases of known or suspected hypertrophy, but they uniformly fail to outline any one of the very few methods which have been proposed for charting such an examination.

A record in writing of the cystoscopic picture has disadvantages. It takes time and effort. It is not conducted in a systematic way and therefore is open to incompleteness and inaccuracy. Hurry Fenwick, as early as 1889, advocated modelling in wax the memory picture of the vesical neck after cystoscopy so as to have a permanent record. Hugh Hampton Young, in 1903, proposed a chart of eight cystoscopic fields arranged in a circle by which the circumference of the vesical neck could be outlined. The necessity of additional views to obviate making two or three diagrams of the one case soon became apparent and in 1904, the method was elaborated by him to its present complete and accurate form¹ (fig. 1). Cunningham, in 1905, devised a

¹ It is recognized that the chart proposed below is nothing more than an adaptation of the principles so clearly presented by Young.

diagram (fig. 2) for the purpose of charting both the shape of the vesical orifice and the length and distortion of the prostatic urethra. From these facts he modelled in wax the actual size and shape of the prostate.

The interpretation of the changes produced at the vesical orifice by hypertrophy is not simple. It depends upon an exact determination of the number, depth and relative position of grooves or sulci and of the size and shape of the lobes forming them. The relation of lobe surfaces and sulci to the trigone and ureteral orifices is of value. Only a small portion of the vesical

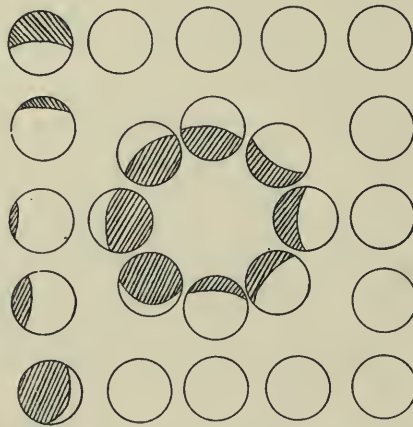


FIG. 1. YOUNG'S CHART. MIDDLE LOBE HYPERTROPHY

Shaft of the instrument in the sulcus to the right of the median lobe (compare fig. 7).

orifice was visible at one time but by rotating the instrument the whole circumference may be examined and a composite picture of it completed. The views are seen at right angles and the instrument pushed in or pulled out as necessary to keep the prostatic and vesical margin in half of the field with neighboring bladder wall in the other half. Interpretations of such a composite picture have been found to be more accurate and practical than either retrograde cystoscopy by means of special instruments which look back along their own shafts, (Young, Nitze, Schlagintweit) or examinations through suprapubic tro-

cars which carry lenses through the Space of Retzius into the bladder (Kraske, Fenwick).

Two factors in particular render complex and confusing the seemingly simple procedure of cystoscopic interpretation. Confusion in the interpretation of the size of the intravesical lobes is a common error. This is due to the fact that the relative size of the image in any cystoscopic field will vary with the distance

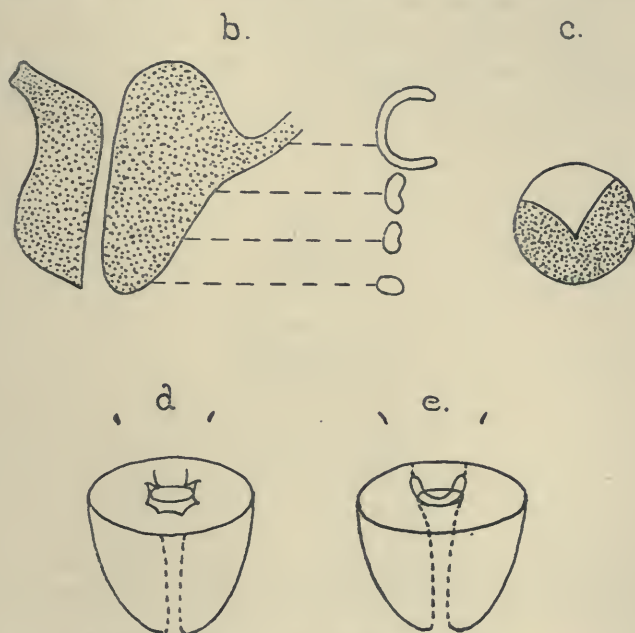


FIG. 2. CUNNINGHAM'S CHART. MIDDLE LOBE HYPERTROPHY

of the lens from the object. The orifice of a ureter through an instrument held in close proximity appears crater-like and the distorted ureteral papilla may completely fill the field. If the lens is elevated the ureteral outline becomes smaller and more distinct. With increase in focal distance detail diminishes and the ridge and papilla appear flattened out on a level with the bladder wall while the orifice diminishes in size to a mere pin point and the cystoscopic field enlarges sufficiently to image both orifices and the whole interureteric ridge (fig. 3).

The cystoscope, when inserted into a bladder with intravesical hypertrophy, may take one of three positions with respect to any particular lobe. It may slip into a sulcus to one or the other side of the lobe, or it may slide in on top of the lobe. In middle lobe hypertrophy the diagnosis is simple if the shaft overrides the lobe and remains upon the summit of the lobe when the instrument is rotated to obtain the different views. But if the shaft takes up a position in the right sulcus and remains in this position throughout the examination, the left ureter and left vesical margin would not be seen on account of the middle lobe being in the way. Analogous possibilities of

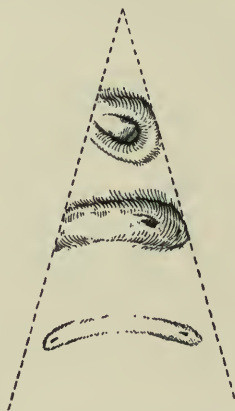


FIG. 3. DIAGRAMMATIC REPRESENTATION OF DIFFERENCES IN SIZE OF URETERAL ORIFICE IN NEAR, MID AND FAR POSITIONS OF THE CYSTOSCOPE

error will hold for anterior lobe hypertrophy or for either lateral lobe, and in the combination hypertrophies unintelligible confusion may arise *unless the position of the cystoscope is controlled by manipulation.*

The following chart and the method proposed for its use will correct the errors of interpretation from the above two factors by insuring a systematic manipulation of the cystoscope. Three main positions (fig. 4) near, mid and far, for each octant of the vesical orifice are sufficient. The complete chart (fig. 5) makes possible the recording of 32 different views of the vesical orifice. The inner circle of eight cystoscopic fields represents the views

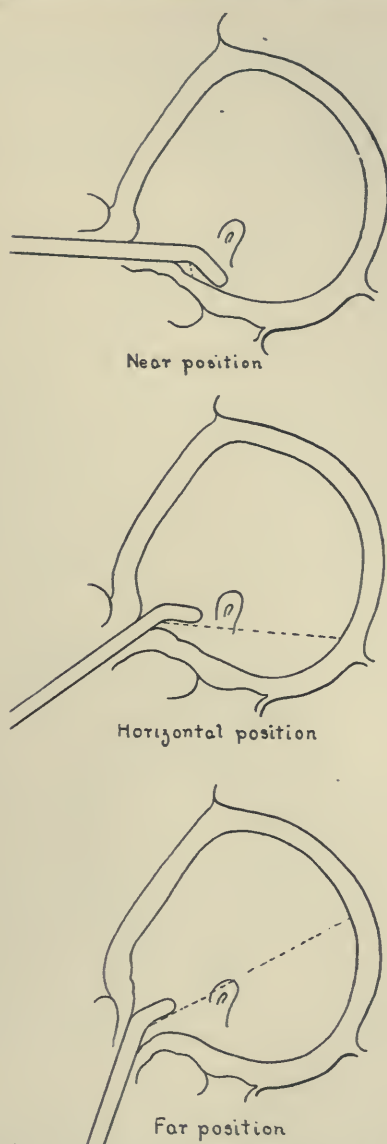


FIG. 4. ILLUSTRATION OF THE RANGE OF MANIPULATION OF THE CYSTOSCOPE
IN THE POSTERIOR POSITION

Similar range of movement is possible for each octant; anterior R. and L.
anterior, and posterior oblique, and R. and L. lateral.

of the vesical orifice with the instrument in the near position for each octant, the middle circle with connecting lines is for charting the eight fields with the instrument held horizontally and the outer circle represents each octant with the cystoscope held with its lens in the far position respectively. The posterior

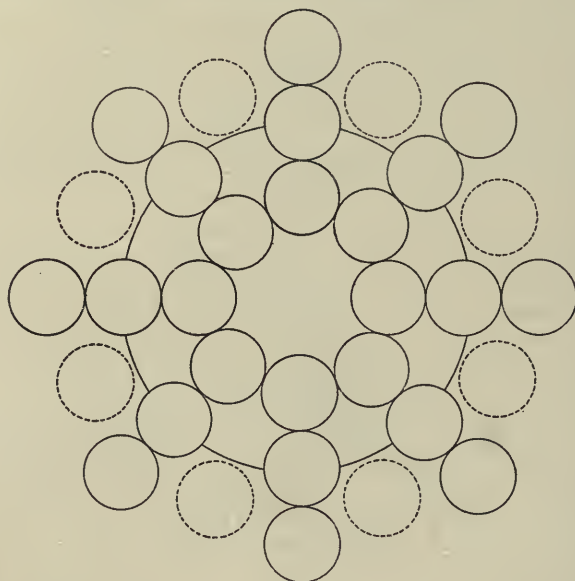


FIG. 5. CHART FOR RECORDING A CYSTOSCOPIC STUDY OF THE VESICAL ORIFICE AND BLADDER

The three circles of each radius represent the views of that particular portion of the circumference with the instrument held in the near, mid and far positions. *A*, anterior; *P*, posterior; *L. L.*, left lateral; *R. L.*, right lateral; *R. A. O.* and *L. A. O.*, the right and left anterior oblique and *R. P. O.* and *L. P. O.*, the right and left posterior oblique octants. The dotted circles serve the double purpose of recording additional views of the prostatic orifice that are obtained upon manipulation, and of indicating accurately the location in the bladder of objects, such as stone, tumor or diverticulum.

margin is first examined through the changes in position of the shaft (fig. 4) near, mid and far which is inserted or retracted as necessary to keep the vesical margin in the field, and the maneuver repeated as often as desired in order to get a clear idea of the changes of the visual fields with changes of position. The instrument is then rotated 45 degrees and the near, mid

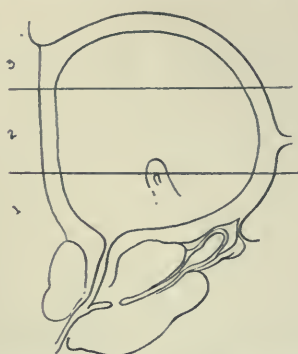


FIG. 6. DIVISION OF THE BLADDER INTO THREE ZONES

1, Lower (cervical) zone; 2, middle (equatorial) zone; 3, upper (fundal) zone. Each zone is divided into eight meridional segments, corresponding to the octants of the vesical orifice. The position of an object in any part of the bladder is indicated by being drawn in a plain or dotted circle (connected by line to proper plain circle) which corresponds to the position of the cystoscope, and the zone in which it lies indicated by the numbers 1, (cervical), 2 (equatorial), 3 (fundal).

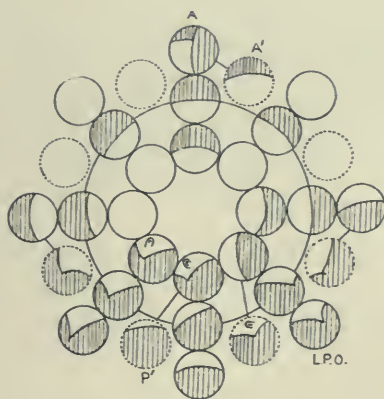


FIG. 7. CHART OF MEDIAN LOBE HYPERTROPHY

The shaft of cystoscope lies by choice in right sulcus. Upon depression of the beak in the posterior octant a notch is seen as the shaft falls into this sulcus. By manipulation it can be made to override the lobe and view in P' is obtained. In the near view of the left posterior oblique position the middle lobe tends to get in the way but the shaft can be manipulated into the left sulcus giving picture in $L. P. O.$ In the anterior octant, far position, the middle lobe rises by the side of the shaft giving the appearance of a notch, A , but manipulation keeps the middle lobe beneath the shaft and view A' shows no notch and therefore no bilateral lobe hypertrophy. In the left lateral, far position, the middle lobe tends to obscure the true vesical margin.

and far positions charted for the posterior oblique octant, and so on, until the whole vesical margin has been examined through the manipulated changes of position for each octant.

The accessory fields on the chart (in dotted lines) serve a double purpose. When the shaft of the cystoscope takes a different course relative to an intravesical lobe upon repetition of a certain movement a quite dissimilar view for the same octant

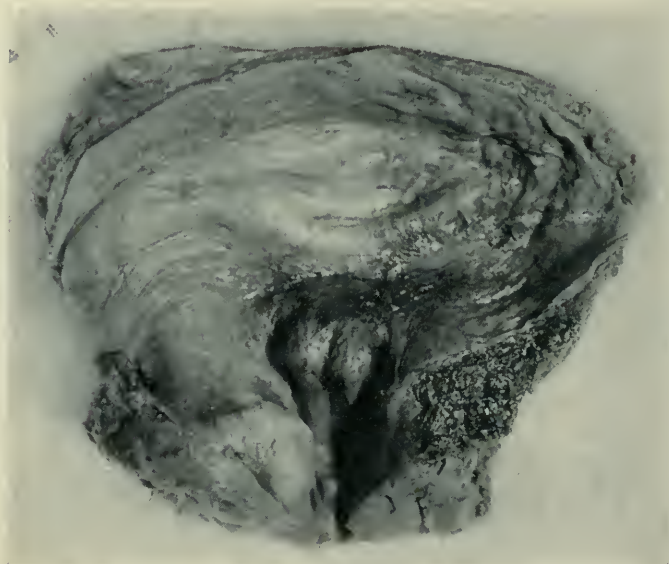


FIG. 8. PHOTOGRAPH OF A SMALL MEDIUM AND BILATERAL LOBE PROSTATIC HYPERTROPHY (AUTOPSY SPECIMEN)

Death due to cardiac and pulmonary complications. The urinary symptoms were negligible. There was no urinary residual.

and position will be obtained. An effort to demonstrate this difference should be made by manipulation. When demonstrated it can be readily charted in a dotted circle and the relationship indicated by a line from this circle to the corresponding octant and position. For example, in the case of a middle lobe hypertrophy, if the shaft of the instrument should fall by choice into the left sulcus of the lobe, in examining the anterior margin, this lobe may appear in the right side of the field and

give the impression of a pronounced anterior sulcus which would indicate bilateral hypertrophy. By manipulation the shaft can be made to remain upon the summit of the lobe or to fall into the right sulcus, either of which positions will quickly demonstrate the true condition. The dotted circles enable one to make an accurate record.

The manipulated changes of position can be very quickly executed, and where no change of view occurs, only one picture

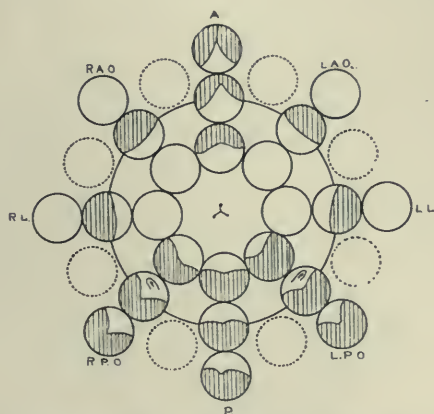


FIG. 9. CYSTOSCOPIC CHART MADE SEVEN WEEKS BEFORE DEATH OF THE CASE WITH PHOTOGRAPH SHOWN IN FIGURE 8

The ureteral orifices are seen in the horizontal position but not in the near or far. (In a normal bladder, without hypertrophy, they would be seen in the middle and far but not in the near. In a larger hypertrophy they might be seen in the near but not in the horizontal and far. In a still larger hypertrophy, figure 11, they are not seen in any position). The shaft of the instrument takes a position upon the summit of the middle lobe and does not tend to lie in either sulcus, and there is no change of view by manipulation. These findings indicate a small sized hypertrophy.

of the octant need be charted. For convenience of routine this one picture is charted in the middle group of circles, with the connecting lines, for which the instrument is held horizontally.

The second purpose of the 8 dotted fields is to serve for charting conditions of the bladder itself. If the bladder be arbitrarily divided into 3 zones, figure 6, and each zone subdivided into meridional segments of 45 degrees, which correspond to the

octants of the vesical neck, there will be 24 meridional segments, 8 each for the 3 zones. The cervical, equatorial and fundal zones correspond to the near, mid and far positions respectively of the diagram, and the 8 meridional segments of each zone are a continuation of their respective octant at the vesical neck. An object can be diagrammed therefore in that circle corre-

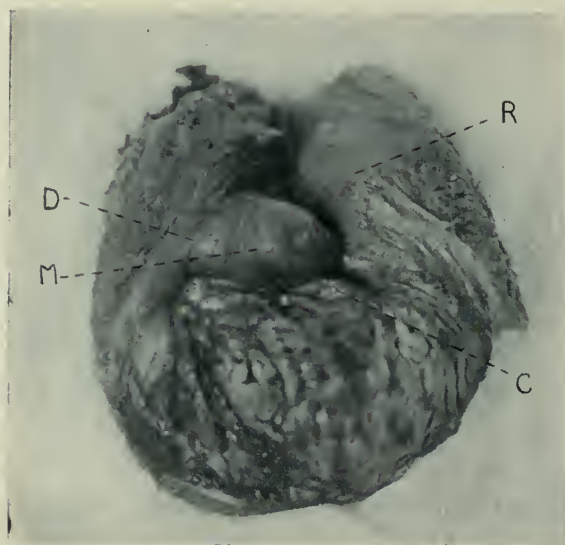


FIG. 10. PHOTOGRAPH OF A LARGE MIDDLE AND BILATERAL LOBE HYPERTROPHY (AUTOPSY SPECIMEN)

Death due to pneumonia, bilateral pyelonephritis, ureteritis and cystitis. An early cystostomy for drainage was done without benefit. *R*, right lateral lobe; *M*, pedunculated middle lobe; *C*, both ureters with the interureteric ridge lie deeply behind the middle lobe; *D*, position in the left sulcus which the instrument tends to take because of the larger right lateral lobe.

sponding to the position in which the cystoscope is held at the time or, if the prostatic views are to be charted also, the object is drawn in an adjoining accessory circle and its position and relationship accurately indicated by connecting this circle to the proper octant and position. To thoroughly inspect an object in the bladder it is necessary, of course, to insert the instrument beyond the vesical neck and to view it from many different

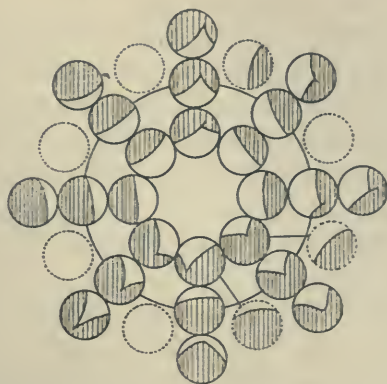


FIG. 11. CYSTOSCOPIC CHART OF THE CASE WITH PHOTOGRAPH SHOWN IN FIGURE 10

Neither of the ureteral orifices nor the trigone could be seen upon manipulation of the cystoscope. The shaft of the instrument falls in the right sulcus only when depressed as the left lateral lobe is smaller than the right. The middle lobe is seen in positions *A* and *L* and is also partly fused with the median. These findings indicate a large hypertrophy.

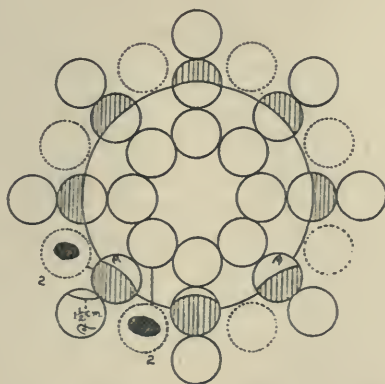


FIG. 12. CHART OF CASE, P. C. 836

With large diverticulum of the bladder the orifice of which lies about 1.5 cm. above the left ureteral orifice and measures about 6 by 8 mm. in size. The drawings in dotted circles show general shape and changes in size for the near and horizontal positions in the right posterior oblique octant. The number 2 indicates its location in the median zone of the bladder.

angles. The accessory circles when used for the purpose of charting objects in the bladder indicate the exact position of the cystoscope from which it is drawn with respect to rotation and to elevation or depression. From this is easily interpreted the location of the object in one or more of the eight meridional segments and its size from variations seen in the mid, near or far position of the lens. The particular zone in which the object lies is quickly recorded by placing the number 1, 2 or 3 beside the plain or dotted circle to indicate the cervical, equatorial or fundal zone respectively. The two purposes of the dotted circles therefore are quite distinct and readily interpreted.

It is believed that the chart will insure systematic thoroughness in cystoscopic examinations and will materially simplify their interpretation. It gives a diagrammatic moving picture film of the vesical neck and bladder. In the accompanying diagrams are illustrated a middle lobe, a small and a large middle and bilateral lobe hypertrophy, and a diverticulum of the bladder.

ABSORPTION FROM THE RENAL PELVIS IN HYDRO- NEPHROSIS DUE TO PERMANENT AND COM- PLETE OCCLUSION OF THE URETER

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Under normal conditions, absorption from the renal pelvis does not occur because of the continuous outflow of urine from the renal tubules. If, however, an acute inflammatory process be present, as in acute pyelitis, the mucous membrane of the pelvis becomes swollen, reddened and edematous and absorption takes place, as is evidenced clinically by elevation of temperature and chills. These clinical manifestations may be due to the absorption of urine and bacterial toxins through the blood vessels or lymphatics of the renal pelvic mucosa directly, or, as will be shown later, the absorption of urine and bacterial toxins retained in the uriniferous tubules may take place. The retention of the urine and bacterial toxins in this instance is due to the probably complete occlusion of the collecting tubules by the swelling and edema of the mucosa covering the papillae. This latter fact may also account for the numerous instances in which pyelo-nephritis is concomitant with or follows an acute pyelitis. Again in acute pyelitis the inflammatory process involves the pelvic mucosa as a whole and often even that of the upper portion of the ureter. The swelling of the mucous membrane of the ureter-pelvic juncture may also be considered a factor in producing the back pressure so necessary for absorption by the above mentioned path.

If the absorption occurs from the tubules, it is directly comparable to absorption taking place after complete ligation of the ureter. In the latter instance the kidney continues to secrete urine against increasing pressure at a normal or an increased rate

for some time. After complete ligation of the ureter, there is congestion of all the renal vessels, the pelvis becomes fully distended with urine, and this is followed by a marked increase in the intratubular pressure as far as the glomeruli. This is strikingly demonstrated by introducing a small quantity of India ink (0.3 cc. or more) into the ureter by gravity and ligating the ureter. If the animal be sacrificed half an hour later and the kidney sectioned, the particles of ink can be found in the collecting tubules, the distal convoluted tubules, the ascending and descending limbs of Henle's loop, the proximal convoluted tubules, the capsule of Bowman, in the spaces between the tufts of the capillaries of the glomeruli, and in the capillaries themselves. In none of our sections have we been able to find any red blood cells in the tubules or any evidence of ruptured blood vessels through which the absorption could have taken place. The remaining renal blood vessels, although greatly engorged, may show little if any India ink in them. These facts and findings seem to us to demonstrate conclusively that a path of absorption is by way of the tubules and through the glomeruli into the blood stream.

If the particles of India ink in the blood stream were due to a rupture of a tubule into the blood vessel, there would be much more ink in the blood vessel than in the tubule but exactly the reverse is true. Again, the pressure in the blood vessels is higher than the pressure in the tubules and this would lead to the supposition that if any rupture were present, it would be from the blood vessels into the tubules, rather than in the opposite direction. Therefore the particles of India ink apparently travel up the tubules and through the endothelial spaces into the capillaries of the glomeruli, thence by the blood stream to the opposite kidney and the other organs of the body. Particles of ink were found in the liver, lungs, spleen, pancreas and the opposite kidney in animals sacrificed in one half hour from the time of injection. In the opposite kidney particles of India ink were found in the blood vessels, in the capillaries of the glomeruli, in the epithelium of the convoluted tubules and in the lumina of the tubules.

In the kidney from which the absorption took place, no particles of India ink were found in the tubular epithelium, demonstrating that the path of absorption is by way of the glomerular capillaries. This rapid absorption from the renal pelvis after complete obstruction to the ureter was also demonstrated by the use of such soluble dyes as phenolsulphonephthalein and indigo carmine and shows that any substance retained in the renal pelvis may be rapidly absorbed and distributed throughout the body.

David (1) in a recent publication on "Ascending Urinary Infections" states that "Evidence is presented to show that ascending bacillus coli infections of the upper urinary tract from the bladder travel most frequently by the lumen of the ureter." It seems probable that the aforementioned path of absorption is in reality but a continuation of that which is found to be true of the ureter. This is clearly demonstrated in fulminating cases of pyelo-nephritis where the obstruction is in the lower urinary tract.

Keyes (2), in experimental studies of the injury caused by pyelography, found that after he had injected collargol into the pelvis of one kidney, it was found in the tubules, blood vessels and glomeruli of the injected kidney as well as in the blood vessels and glomeruli of the opposite kidney. He assumed that the path of absorption was by way of the blood vessels and lymphatics of the injected kidney.

Eisendrath (3) made the same observations with collargol demonstrating that collargol enters the blood stream by rupture of the tubules into the blood vessels. In his experiments, however, he injected the collargol under pressure and in some instances in amounts exceeding the pelvic capacity. Therefore, from our experiments, it seems probable that he forced collargol into the renal parenchyma and that naturally some of the tubules did rupture into the blood vessels from over distention.

Macht (4), in his recent work on absorption from the bladder, failed to demonstrate any absorption from the bladder which is lined with transitional epithelium of the same character as that lining the pelvis of the kidney.

In the following experiments we have attempted to demonstrate not only the path but also the rate of absorption by the intro-

duction of a soluble dye as phenolsulphonephthalein into the pelvis of the obstructed kidney and estimating its hourly secretion by the unobstructed kidney.

Method of procedure. Under ether anesthesia, the kidney and ureter are exposed through a lumbar incision, care being taken in freeing the latter from surrounding tissues to avoid injuring the periureteral vessels. The ureter is now securely ligated 1.5 cm. below the uretero-pelvic junction, the needle introduced into the ureteral lumen and the solution to be introduced into the pelvis allowed to run in by gravity. Over distention of the pelvis was prevented by never elevating the burette containing the solution beyond 6 inches above the body of the animal. In four instances in which the solution was introduced by means of a syringe, the results were so variable that it seems probable that some of the fluid was forced into the renal parenchyma. The amount of solution introduced sufficient to distend the renal pelvis by the method just outlined were of necessity subject to considerable variation because of the presence of variable amounts of urine in the pelvis, dependent upon the rate of renal secretion. For this reason the concentration of the solutions introduced varied considerably. Following distention of the pelvis to its capacity, the ligature previously placed proximal to the needle was tied as the needle was withdrawn. The ureter was now replaced in its normal position and the wound closed with silk ligatures.

This procedure was carried out on eighteen animals followed by a second operation done in five instances. The second operation was carried out on dogs 1, 5, 6, 12 and 15. In these instances the left kidney was exposed transperitoneally through a left rectus incision. Large hydronephroses with extensive venous collateral circulation were found in each case. In none of our cases did atrophy of the kidney follow complete permanent occlusion of the ureter, thus confirming the results of Barney's work (5) as well as previous work of Burns and Hopkins (6).

In dogs 4, 5, 7, 12 and 15, subcutaneous infusions of warm normal salt solution from 100 to 200 cc. were given with the view of increasing the urinary output and although this pro-

cedure increased temporarily the amount of urine secreted, it did not materially increase the output of phenolsulphonephthalein.

The substances used in this series of experiments were: (1) Solutions of phenolsulphonephthalein (6 mgm. to 1 cc.); (2) Aqueous suspensions of indigo-carmin, 4 per cent; (3) India ink.

*Phenolsulphonephthalein was injected into the renal pelvis of seven animals, previously unoperated, using a syringe in two instances and the gravity method in the remainder. This dye was also injected by gravity into five hydronephrotic kidneys varying from a few cubic centimeters to several hundred cubic centimeters capacity and from twenty-four days to three and one-half months duration.

The amount of dye used in the early hydronephroses varied from 0.3 cc. to 1 cc. of the standard solution. In the more advanced forms, however, as much as 100 cc. of standard solution were introduced into the renal pelvis. In one instance a very concentrated solution (180 mgm. in 7 cc.) was used but the output by the other kidney was relatively the same. The estimations of the hourly output of the dye, as shown in the curve, are made solely upon the actual amount of the dye employed in each case.

The output of the dye varied in previously unoperated dogs from a mere trace in four hours, where the gravity method was used, to 40 per cent in four hours where the syringe was employed, this large output in the latter case being due to the forcing of the dye into the tubules and circulation.

The average output where the gravity method was used in dogs previously unoperated seems to be from a trace the first hour, 2 to 3 per cent the second hour, 3 to 5 per cent the third hour, a trace to 5 per cent the fourth hour, a trace to 5 per cent in the fifth hour and as much as 20 per cent in the following eighteen hours. In a few instances the rate of secretion diminished after the third hour and the output was greatly prolonged. The larger hydronephroses showed approximately the same output for twenty-four hours but the secretion was much prolonged, the dogs with the larger hydronephroses secreting phenolsulphonephthalein long after the less advanced case had reached his maximum and had ceased to secrete any of the dye.

In experiment 1, 1 cc. of standard solution of phenolsulphonephthalein was injected into the ureter with a Record syringe. The animal was catheterized at the end of an hour and ten minutes, the output of the dye being 10 per cent of the amount injected. During the second hour 16 per cent was obtained while for the third and fourth hours the percentage of secretion was 9 and 5 per cent respectively, a total of 40 per cent in four hours and ten minutes. Later experiments have proved that the large hourly output by this animal in this experiment was due to the fact that the renal pelvis was overdilated with solution by use of the syringe and it is most probable that the dye was forced into the renal parenchyma and the circulation.

One month later, this dog was operated upon again (experiment 6). The exposure was made through an abdominal incision and a large hydronephrosis with extensive collateral venous circulation found. Two cubic centimeters of urine were withdrawn and 1 cc. of phenolsulphonephthalein injected into the sac by gravity. The animal was catheterized at hourly intervals for five hours and at the end of eighteen hours. To this last specimen was added the urine voided during the interval. No dye was present in any of these specimens. The absence of absorption and re-excretion in this instance was probably due to the fact that the hydronephrotic sac was not emptied and as a result the phenolsulphonephthalein was so greatly diluted by the retained urine that practically none of it was brought into contact with the absorbing surfaces.

In experiment 15, dog 12, at the first operation, the secretion was less than 2 per cent each hour for five hours. The second operation, fifty days later revealed a large hydronephrosis from which was drained 60 cc. of infected urine. Fifty cubic centimeters of standard solution of phenolsulphonephthalein were then injected by gravity. The secretion of the dye was as follows, for the first hour 0.6 per cent, for the second hour 1 per cent, for the third hour 2 per cent, for the fourth hour 1 per cent, and for the fifth hour 5 per cent. This dog was killed and autopsied thirty days later. It had continued to secrete the dye throughout this entire period and at autopsy the hydrone-

phrotic sac contained 60 cc. of infected urine which still contained appreciable amounts of the dye. The pressure in the sac at autopsy was 160 mm. of water.

In experiment 19, dog 15, there was found a large hydronephrosis of one hundred and eight days duration. At the operation 140 cc. of urine was withdrawn and 100 cc. of phenolsulphonephthalein injected by gravity. The output the first, second, third, fourth and fifth hour was but a trace at each reading. This dog also continued to secrete the dye at this slow rate for the next thirty days, at which time he was killed and autopsied. A large hydronephrosis containing 400 cc. of urine was found. This urine contained phenolsulphonephthalein in appreciable amounts. The pressure in the hydronephrotic sac was 130 mm. of water. The kidney was entirely destroyed and only a thin walled sac remained. The wall of the hydronephrotic sac was composed almost entirely of fibrous tissue, as is the case in long standing hydronephroses, where the renal parenchyma is destroyed by pressure atrophy. It should be noted that when the sac was emptied at operation, it was not possible to replace by gravity as much fluid as was withdrawn.

It is evident that the prolonged secretion was due to the slow absorption of the dye owing to its dilution by the urine in the hydronephrotic sac, the remaining remnants of renal tissue continuing to secrete against increasing pressure for a long time.

In experiment 9, dog 5, there was found a large hydronephrosis of twenty-four days duration. Thirty-four cubic centimeters of infected urine was withdrawn and 22.5 cc. of standard solution of phenolsulphonephthalein was injected by gravity and 150 cc. normal salt solution given subcutaneously. The output for the first hour was only a trace, for the second hour 1 per cent, for the third hour 1 per cent, and for the fourth hour 1 per cent. This dog died on the ninth day from peritonitis following rupture of the sac.

INDIGO-CARMINE

Phenolsulphonephthalein is not the only soluble dye absorbed from the renal pelvis and secreted by the other kidney. Studies of the absorption of indigo-carmin were made on two animals, in one of which the syringe was used and in the other instance the gravity method of injection.

In experiment 2, dog 2, 1 cc. of 4 per cent aqueous suspension of indigo-carmin was injected into the pelvis and the animal killed in one and one-half hours and autopsied, the dye having appeared in the urine coming from the other kidney. Sections were made and the dye found in both kidneys but in insufficient amounts to permit its path to be traced.

In experiment 10, dog 8, 0.3 cc. of 4 per cent aqueous suspension of indigo-carmin was injected by the gravity method and the dog killed in three hours and autopsied. The kidney with the ligated ureter weighed 49 grams and the opposite one 29 grams, this increase in weight being due to retained urine and congestion. On section the dye was found in small amounts in both kidneys.

INDIA INK

Failing to trace the path of absorption by the use of indigo-carmin, india ink was used in a series of nine experiments, the injection being made by gravity in seven and with the syringe in two instances. In all of these animals the ureter was completely ligated before the ink was injected. The seven animals were killed at intervals of from thirty minutes to twenty-four hours after the injection and autopsied and sections were made from both kidneys, liver, spleen, lungs and pancreas. These specimens were embedded in celloidin and the section stained with eosin alone, so as to avoid confusing any granules from the stain with those of india ink. The amount of ink used in these experiments varied from 0.25 cc. to 1 cc. and in no instance was the pelvis forcibly distended with the solution. In every case where the ink was absorbed in amounts sufficient to permit the tracing of its course through the absorbing kidney into the cir-

culatation and through the normal kidney, its presence was demonstrated in the other organs with an extensive capillary circulation, namely, the liver, lungs and spleen.

The particles of ink can be seen distinctly in the collecting tubules, distal convoluted tubules, ascending and descending limbs of the loop of Henle, proximal convoluted tubules, the space between the parietal and visceral layers of Bowman's capsule and between the tufts of the capillaries of the glomeruli themselves. Particles of ink can also be seen in the capillaries of the glomeruli and in the other vessels of the kidney. However, their appearance in these latter vessels is much less marked than in the former. In the normal kidney, the particles of ink are seen mainly in the renal vessels and capillaries of the glomeruli, although some may be found in the epithelial cells of the convoluted tubules and in the lumina of these tubules. These facts seem to demonstrate that the particles of ink ascend the tubules of the absorbing kidney, enter the circulation through the spaces between the endothelial cells of the capillaries of the glomeruli, are carried by the blood stream to the other organs of the body and are secreted by the other kidney, both by the glomeruli and the epithelial cells of the convoluted tubules. It is reasonable to suppose that if particles of ink can travel in this manner, bacteria and other foreign substances can do likewise.

CONCLUSIONS

1. Absorption takes place from the renal pelvis after complete ligation of the ureter.
2. Absorption also takes place from the renal pelvis in long-standing hydronephroses.
3. The path of absorption as demonstrated is by way of the tubules and through the capillaries of the glomeruli.
4. The rate of absorption is prolonged, especially in case of hydronephrosis.
5. The rate of absorption during the first twenty-four hours is frequently the same in long standing hydronephroses as in the acutely distended pelvis.

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PLATE 1

FIG. 1. Photomicrograph showing particles of India Ink ascending the lumina of the collecting tubules of the injected kidney.

FIG. 2. Photomicrograph showing particles of India Ink ascending the lumina of the distal convoluted tubules, the ascending and descending limbs of the Loop of Henle, and the proximal convoluted tubules of the injected kidney.

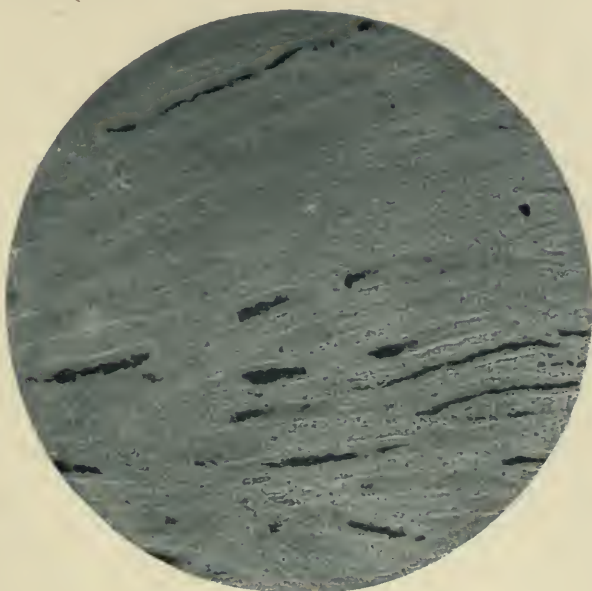


FIG. 1

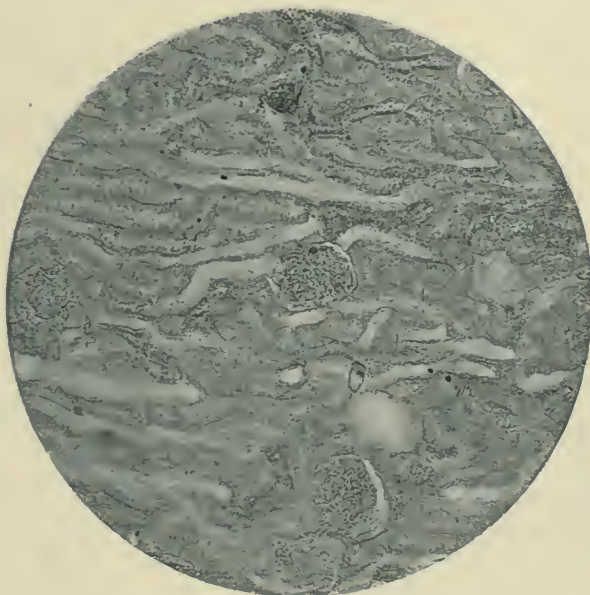


FIG. 2

PLATE 2

FIG. 3. Photomicrograph showing particles of India Ink in the space between the parietal and visceral layers of Bowman's Capsule and between the tufts of the capillaries of the glomeruli themselves in the injected kidney.

FIG. 4. Photomicrograph showing particles of India Ink in the glomeruli and epithelial cells of the convoluted tubules of the opposite kidney to the one injected.

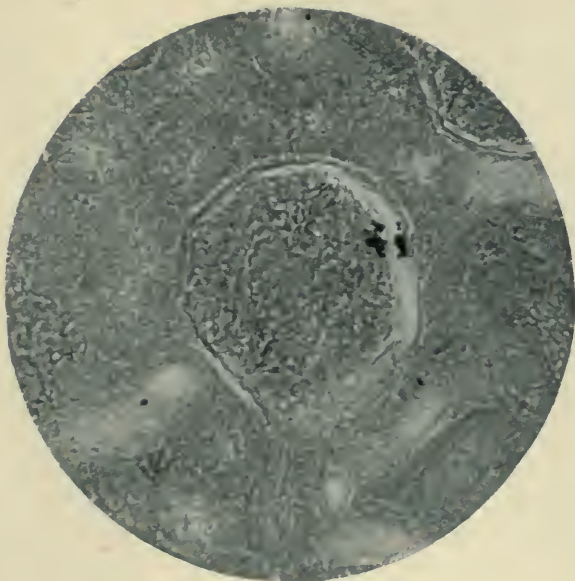


FIG. 3

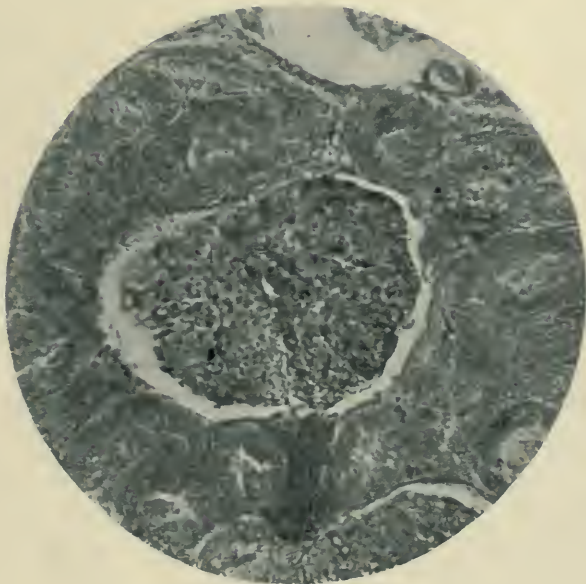


FIG. 4

THE USE OF A PROVOCATIVE VACCINE IN DETERMINING THE CURE OF GONORRHOEAL URETHRITIS¹

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One of the most difficult problems which is encountered in the management of a case of gonorrhoea is to determine when the case is cured. Not only is this important from the standpoint of the patient himself but the evils which follow in the wake of an uncured case, discharged as cured and affecting innocent persons, make the question a vital one. The absence of clinical signs, i.e., the disappearance of the discharge and the filaments in the urine does not prove necessarily that a cure has taken place, for this evidence is frequently falsified by the recurrence of the discharge, crowded with gonococci, when no fresh exposure has occurred.

A number of tests have been devised for the purpose of excluding latent disease but they are faulty. The usual method adopted is to take the patient off all treatment after his discharge has disappeared and his urine has been clear and free from all filaments for a week to ten days; give him some heavy work or exercise for several days and if there is no recurrence of symptoms, massage the seminal vesicles, prostate, and Cowper's glands and examine the expressed secretion microscopically, a smear being taken from the urethra the following morning. If the findings are negative for pathological elements and there is no recurrence of symptoms within the next three days a large sound is passed. If the smear taken the next morning is negative for the gonococcus, as soon as any irritation that the sound may have produced has subsided, the patient is told he is cured.

¹ Report No. 7, Gonorrhea Service, Canadian Hospital, Etchinghill, England. Preliminary report of 100 cases.

Any one who has treated a number of cases of gonorrhoea will readily acquiesce in the statement that this method at best is fallacious. Witness the number of relapses that supervene and try the patience of the surgeon and the confidence of the patient in his medical advisor. Even if the urine passed, after the prostatic massage and containing the prostatic, vesicular and Cowpral secretions, and the secretion from the posterior urethra is centrifuged and cultured the difficulty of growing the gonococcus is so great that a negative result is unreliable. Making a cystourethroscopic examination of whole genito-urinary tract is also not final for I have seen urethrae apparently normal in which later there has been a relapse with all the symptoms of a specific urethritis.

Several other means have been devised to produce an irritation whereby the deeply implanted gonococci will be carried into the lumen of the urethra with an exacerbation of symptoms and the appearance of the organism in a smear. The imbibition of alcohol, sexual intercourse with a condom and the injection of silver-nitrate, 1-500 are the most commonly used. The first two are impracticable in the army and are not to be lightly recommended in private practice on account of the unfortunate results that may follow. The injection or irrigation with silver nitrate is perhaps to date the most reliable test but there are grave objections to its use. The urethra is already irritated sufficiently by treatment and by its struggle with the gonococcus and to place upon the newly recovered tissue the strain of combating a strong chemical irritant may do more harm than good. If the case is cured of gonorrhoea and the smear remains negative for the organism, the urethra has to recover from its chemical inflammation. Should the case be only apparently cured, the urethra will have to contend with a re-infection superimposed upon a damaged mucous membrane and this will make the relapse more difficult to treat.

For some time it has been known that an injection of a gonococcus vaccine has an effect in altering the clinical symptoms. Following such an injection the added endotoxin is too much for the defensive immunity produced by the body against the

original infection so that, for the time being, the defenses are overwhelmed. Resistance is lowered and the gonococcus is enabled to proliferate in peace. This negative phase lasts forty-eight to seventy-two hours and is followed by a positive phase in which the defenses of the body are stimulated and produce sufficient antibodies to neutralize the added toxin plus the toxin absorbed from the original infection. During the negative phase should any gonococci be hidden in the depth of the tissue they will grow and probably break through to the surface of the mucous membrane.

In the combat between the gonococcus and the body the promotion of free drainage of the urethra and its glandular structures and the production of congestion whereby the bactericidal substances of the blood are marshalled to the point of invasion are valuable aids in the treatment. The adoption of these measures together with the maintenance of bodily and mental health constitute however the sum total of our present therapy. The gonococcal powers of the body are the first, second and third line of defense but, as the defensive powers against the invading gonococci are strengthened so also are the defensive powers of the gonococci against the body fluids. In the end the body prevails but deep down in the tissues a few gonococci may still lurk, practically immune against the resistance of the host but potentially as harmful as ever. When the general resistance is lowered they may burst forth into the urethra and a relapse occurs. While they are latent the symptoms and signs of the disease are absent.

Any condition tending to lower the specific bodily resistance may cause a relapse of the disease. To produce this a single injection of a potent gonococcus vaccine has been recommended by several observers, notably McDonagh (1) and Asch (2). The former states that a provocative vaccine will alter the symptoms either positively or negatively but that the test is unreliable. The latter uses a single large dose and follows it up by a urethroscopic examination to discover if any new lesions are formed. Experimenting with a single large dose it was found that much depends upon the acuteness of the observer and for that reason

the test, as a general routine, is unreliable. It was observed, however, that smears taken on the three or four mornings following the dose of vaccine frequently gave a result positive for the gonococci in cases apparently cured. If a single dose of gonococcus vaccine will produce a negative phase of sufficient intensity to enable the latent gonococci to break out of their hiding places and re-infect the urethra sufficiently to produce a positive smear, it is reasonable to expect that if the specific resistance be lowered still further the same result can be obtained in nearly every case. To do this the most advantageous method appeared to be to give a dose one day followed by a dose the next. The second dose would still further increase the negative phase produced by the first dose. To use two large doses would be inadvisable on account of the severe general reaction produced and the possibility of extending the disease to structures not already involved.

Consequently it was decided to use two small doses on successive mornings. In no cases did the vaccine produce a general reaction nor was any discomfort caused to the patient and no complications followed its use. The method adopted is as follows: On the morning of the first day a dose of three million of polyvalent gonococcal vaccine is administered subcutaneously and at the same time the seminal vesicles, prostate and Cowper's glands are thoroughly massaged to liberate any toxins confined in them. The patient is then instructed to hold his water from midnight of that night until a smear is taken the next morning and to do the same for each successive night until four smears have been obtained. On the morning of the second day a dose of five million of the vaccine is administered. Should the case still be infected with the gonococcus, a positive smear may be obtained on one of the four mornings. Should there be no infection with the gonococcus the smear will remain negative for that organism.

One hundred consecutive cases are tabulated herewith. Table 1 deals with the cases which have a positive smear. The cases comprising table 2 gave negative results. As these cases developed positive gonococcal smears at no subsequent time so far as

can be traced to date they may be considered as free from infection at the time of the administration of the provocative vaccine.

The preponderance of cases giving a negative result over those giving a positive result is due to the fact that practically all these cases were considered to be clinically cured and ready for discharge from the hospital. The positive results were those cases which would have been liable to relapse.

The four unreliable results, i.e., smears negative after provocative vaccine but positive at some later date without reinfection are presented in more or less detail. A reason that a satisfactory result was not obtained in these cases has not as yet been determined. All four cases were atypical in character and may have been infected by a strain of gonococcus not included in the vaccine. A comparison of columns d and e, table 1 shows that besides producing a positive smear the provocative vaccine usually produces a distinct alteration of symptoms in the uncured cases. To judge of results by the alteration of symptoms, however, is unreliable, as in certain cases the clinical symptoms remain unaltered and a positive smear, swarming with gonococci, but only containing a few pus cells, is obtained.

To determine whether results similar to those obtained by provocative vaccine occurred in the course of the ordinary case, a number of cases have had a smear taken every morning over a period of time. In all the cases of this series when the smear remained persistently negative a positive was obtained after the provocative injection. A urethroscopic examination, previous to the administration of the provocative vaccine, in those cases which gave a positive smear subsequent to its use, showed an apparently normal urethra, but on being examined again on the fourth or fifth day after the vaccine showed several definite lesions indicative of gonorrhoea.

The provocative vaccine is not only useful in determining whether a patient no longer is infected but also as an aid to diagnosis in cases resembling non-specific urethritis. Used for this purpose it is not as reliable as in determining when a case is cured.

Explanation of following tables

Column (a) Day of disease on which last positive smear was obtained.
 Column (b) Day of disease on which first dose (3 million) of provocative vaccine was given.
 Column (c) Result of first smear taken on the morning after the first dose (3 million) of vaccine.
 Column (d) Result of smear taken on the morning of the second dose (5 million) of vaccine.
 Column (e) Result of third smear.
 Column (f) Result of fourth smear.

Reading of smears:—

Gonococci	+++ numerous gonococci.
	++ gonococci present.
	+ few gonococci present.
	0 gonococci absent.
Pus	+++ numerous pus cells.
	++ pus cells present.
	+ few pus cells.
	0 pus cells absent.
Epith.	+++ numerous squamous epithelial cells.
	++ squamous epithelial cells present.
	+ few squamous epithelial cells present.
	0 squamous epithelial cells absent.
Organisms.	+++ organisms other than gonococci numerous.
	++ organisms other than gonococci present.
	+ few organisms other than gonococci present.
	0 organisms other than gonococci absent.

TABLE I
Positive results after provocative vaccine

CASE NO.	(a) LAST SMEAR	(b) DAY VACCINE GIVEN	(c)				(d)				(e)				(f)			
			GONOCOCCI	PTB	EPITHELIAL	ORGANISM	GONOCOCCI	PTB	EPITHELIAL	ORGANISM	GONOCOCCI	PTB	EPITHELIAL	ORGANISM	GONOCOCCI	PTB	EPITHELIAL	ORGANISM
1	95	198	0	+	+	+	0	+	+	+	+	+	+	0	0	+	0	0
2	28	0	0	0	+	+	0	+	+	0	0	0	0	0	0	0	+	0
3	76	134	0	0	+	+	0	0	+	0	0	0	0	0	0	0	+	0
4	34	65	+	+	0	+	0	0	+	+	0	0	0	0	0	0	+	0
5	10	43	+	+	+	+	0	0	+	0	+	+	+	0	0	0	+	0
6	9	42	0	0	+	+	0	0	+	0	+	+	+	0	0	0	+	0
7	212	245	0	0	+	+	0	0	+	0	+	+	+	0	0	+	+	0
8	0	78	0	0	0	0	0	+	+	0	0	0	+	0	0	+	+	0
9	0	7	0	0	+	+	0	0	+	0	0	0	+	0	0	+	+	0
10	482	548	0	0	+	+	0	0	+	0	0	0	+	0	0	0	0	0
11	130	163	0	0	+	+	0	0	+	0	0	0	+	0	0	0	0	0
12	96	126	0	0	+	+	+	0	0	0	0	0	0	0	+	0	0	0
13	0	53	+	+	0	0	0	0	+	0	0	+	+	0	+	+	0	0
14	0	156	0	0	+	+	0	+	+	0	0	+	+	0	+	+	+	0
15	0	64	0	0	0	0	0	0	+	0	0	0	0	0	0	0	+	0
16	0	226	0	0	0	0	+	+	+	0	0	0	+	0	0	0	+	0
17	0	23	0	0	0	0	+	+	+	0	0	0	+	0	0	0	+	0
18	0	88	0	+	+	+	0	0	+	0	0	0	+	0	0	0	+	0
19	0	116	+	+	+	+	+	+	+	0	0	+	+	0	0	+	+	0
20	0	198	+	+	0	0	+	+	0	0	0	+	0	0	+	+	+	0
21	2	161	+	+	0	0	0	0	0	0	+	+	0	0	+	+	+	0
22	0	40	0	+	+	+	0	+	+	0	0	+	0	0	+	+	+	0
23	0	89	+	+	+	+	+	+	+	0	0	+	+	0	0	+	+	0
24	0	150	+	+	+	+	+	+	+	0	0	+	+	0	0	+	+	0
25	0	31	+	+	+	+	+	+	+	0	0	+	+	0	0	+	+	0
26	381	415	+	+	+	+	0	+	+	0	0	+	+	0	0	+	+	0
			11+		+	+	9+		+		7+				6			

TABLE 2—Continued

CASE NO.	(a)		(b)				(c)				(d)				(e)				(f)			
	LAST SMEAR	DAY VACCINE GIVEN	GONO-	PUS	EPITH.	ORGAN-ISM	GONO-	PUS	EPITH.	ORGAN-ISM	GONO-	PUS	EPITH.	ORGAN-ISM	GONO-	PUS	EPITH.	ORGAN-ISM	GONO-	PUS	EPITH.	ORGAN-ISM
53	0	7	0	+	+	0	0	0	0	+	0	0	0	0	0	0	0	0	0	+	+	+
54	0	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
55	0	41	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
56	0	40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
57	49	81	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
58	129	157	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+
59	0	32	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
60	0	196	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
61	0	6	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
62	0	6	0	+	+	0	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+
63	0	1120	0	0	0	+	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+
64	0	190	0	+	+	0	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+
65	0	51	0	+	+	0	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+
66	0	53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
67	0	61	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+
68	30	54	0	+	+	0	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+
69	0	745	0	+	+	0	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+
70	0	148	0	+	+	0	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	+

The method adopted for determining a cure when a provocative vaccine is used is as follows:—When no clinical evidence of the disease has been present for two weeks and smears are negative for the gonococcus and pus, the patient is taken off treatment. At the end of four or five days he receives a careful massage of prostate, seminal vesicles and Cowper's glands and a provocative vaccine. If all four smears are negative a sound is passed. Should there be no return of symptoms he is considered cured. Should the smears be negative but should a slight recurrence of the symptoms appear, it is advisable to keep him under observation until this has subsided. In civilian practice or where sufficient laboratory facilities are available in the Army a more thorough method should be adopted. The urine passed each morning after the smear is taken should be centrifuged and examined microscopically or cultured. Instead of the passage of a sound a complete cystourethroscopic examination should be made. If all these tests prove negative the patient should be pronounced cured and fit to marry.

Histories of four cases which gave negative smears after provocative vaccine but which subsequently gave a positive smear

Case 1. Private A. Admitted on 93d day of disease as a relapse with both gonorrhoea and syphilis. Smear and fixation both positive. Urethritis complicated by prostatitis, littritis and multiple papillomata. Developed cystitis. Last positive smear previous to administration of vaccine on 217th day of disease. Subsequently he received a course of vaccine treatment with a stock polyvalent vaccine, the course ending on 274th day. Previous to the administration of the course of vaccine the fixation test taken at irregular intervals gave the following results: + neg., +, neg., + neg., but subsequently it was ++. On 296th day of disease the provocative vaccine was administered with the following smears: (1) Gonococci neg., pus neg. epith. neg., org. neg. (2) Gonococci neg., pus neg., epith. +, org. neg. (3) Gonococci neg., pus neg., epith. +, org. neg. (4) Gonococci neg. pus +, epith. +, org. neg.

On the 318th day after an injection of 1-10,000 silver nitrate the smear was gonococci +, pus ++. Since that time he has had one positive smear.

The alteration in the complement fixation would make it appear that the body was not reacting well to the disease. The course of vaccine treatment may have had something to do with the unreliable results obtained.

It is possible that if smears had been taken after the administration of provocative vaccine a positive result might have been obtained.

Case 2. Private C. Admitted on 676th day of the disease with a relapse. Smear positive. Complement fixation positive +++. Prostatitis and stricture of the penile urethra. Last positive smear 733d day. Provocative vaccine administered 764th day. Smears as follows: (1) Gonococci neg., pus neg., epith. +, org. neg. (2) Gonococci neg., pus neg., epith. +, org. neg. (3) Gonococci neg., pus neg., epith. neg., org. neg. (4) Gonococci neg., pus +++, epith. +, org. neg.

The next positive smear on the 802d day following dilation of the stricture. No positive smear since.

Case 3. Private C. R. J. Admitted on the 37th day of disease as transfer from another hospital. Smears negative. Fixation, negative. Clinical symptoms very slight. Slight prostatitis. Provocative vaccine administered 75th day. Smears as follows:—(1) Gonococci neg., pus neg., epith. +, org. neg. (2) Gonococci neg., pus neg., epith. neg., org. neg. (3) Gonococci neg., pus neg., epith. +, org. neg. (4) Gonococci neg., pus ++, epith. ++, org. neg.

Case 4. Corporal E. Admitted on the 34th day after exposure, with syphilis. Received two injections of "606" and one of mercury. On 8th day in hospital developed urethral discharge making an incubation period of 41 days! Smears negative. Fixation, negative. Provocative vaccine administered on 7th day of discharge. Smears as follows: (1) Gonococci neg., pus neg., epith. neg., org. neg. (2) Gonococci neg., pus neg., epith. neg., org. neg. (3) Gonococci neg., pus neg., epith. neg., org. neg. (4) Gonococci neg., pus +, epith. neg., org. neg. about a week subsequent of this date a smear was taken every day. These smears showed pus and secondary organisms until the 62d day of the discharge, when with no alteration in treatment the smear showed gonococci +, pus ++, epith. ++, org. neg.

CONCLUSIONS

1. The provocative vaccine gives a reliable result in 96 per cent of cases when used by the above method. It should not be

relied upon solely, but should be used in conjunction with other routine tests.

2. Besides being valuable to determine when a case is cured, it is useful to differentiate between specific and non-specific urethritis.

3. Its use renders unnecessary the irritation of the urethra produced by strong provocative injections of chemicals.

4. The above technique is particularly adapted to Army treatment as it is a safe, rapid and comparatively reliable method of determining cure.

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THE REMOTE EFFECTS OF ABSORPTION OF URINE FROM THE COLON: A CASE OF TRAUMATIC UNILATERAL URETERO-INTESTINAL ANASTOMOSIS

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In uretero-intestinal anastomosis the problems which have been given the most consideration are the possibility and effect of ascending renal infection, the prevention of hydronephrosis and the practicability of utilizing the large bowel as a urinary reservoir. Very little consideration has been given to the remote effect on the body of the prolonged absorption of urinary products from the bowel.

Operations of implanting the ureter into the bowel are becoming more and more practicable. Much credit is due to Coffey for the development of the modern technique to offset the heretofore extremely dangerous immediate complications of ascending renal infection and the somewhat less immediate complications of occlusion of the ureter and secondary hydronephrosis. From a technical standpoint the implantation of the ureter into the bowel is an accomplished surgical procedure.

A review of the whole subject seems warranted to determine what has been heretofore more or less disregarded, that is, as to what effect on the body this diversion of the urinary stream into the intestinal tract is going to have. We have approached the subject by reviewing the work which has been done on animals, by investigating the cases of congenital anastomosis between the ureter and bowel and by reviewing the clinical cases of uretero-intestinal anastomosis in man which have lived for any considerable length of time.

We have been prompted in carrying out this investigation by a most interesting case, a case which so far as we have been able

to learn is unique in as much as an uretero-intestinal anastomosis resulted from traumatism.

ANIMAL EXPERIMENTS

The literature has been gone over very carefully from the first uretero-intestinal anastomosis done by Gluck and Zeller in 1881 until the present time. Practically all the experimenters have been concerned primarily with the development of a technique for the implantation of the ureter into the intestine. According to Steinke, who in 1909 reviewed the literature of a hundred and thirty-four bilateral implantations, there was an immediate mortality rate of 87 per cent while in seventy-seven unilateral implantations there was a mortality rate of 60 per cent. The longest term of life which we have found recorded has been about two years. This rather brief term of life was not necessarily dependent upon any ill consequences from the uretero-intestinal anastomosis but most of the animals were autopsied to determine what had been the result of various types of implantations. From a review of these earlier experiments there is nothing of value to be learned as to the remote effects on the body of the absorption of urine from the intestinal tract.

The recent work of Baird, Scott and Spencer in this connection is interesting. According to these experimenters if the ureter be implanted into the intestine through a natural duct, hydronephrosis will not result nor will ascending infection take place. They therefore implanted the right ureter into the duodenum through one of the pancreatic ducts in dogs. A number of experiments were conducted and the right kidney in all of these cases seemed to preserve its functional capacity. In order to determine what effect upon the body from absorption of urine from the upper intestinal tract might have, they removed the left kidney in animals in from four to six weeks after the implantation of the right ureter through the pancreatic duct. It was found that in forty-eight hours the dogs, which had previously been well, now showed nausea, vomiting, gradual loss

of appetite, rapid emaciation, gradually sinking into a stuporous condition and dying in a comatose state in from five to seven days. Autopsy showed that death was not due to destruction of the right kidney and they concluded that the substances in the urine which when retained give rise to the symptoms of nephritis, can be absorbed from the intestine and that whatever these substances are, they are taken into the blood from the intestinal tract unchanged in their passage through the intestinal mucosa. They concluded that the entire urinary output cannot be drained into the upper intestinal tract as the absorption gives toxic symptoms ending in death usually within twelve days.

CONGENITAL CASES OF URETERS OPENING INTO THE BOWEL

The splendid work of Prof. George S. Huntington on the genetic interpretation of variations of the genito-urinary tract has pointed out that the gross anomalies of the kidney and ureter met with in adults are explained by the occurrence of very minor disturbances in the normal processes of development, and that from a knowledge of the development of the genito-urinary tract one can predict the possible variations to be encountered in postnatal life. From a study of early human embryos it is not difficult to understand that in the early stages, shortly after the Wolffian duct has joined the cloaca, that the descent of the lateral folds which divide the cloaca into the bladder and intestine might take place at such a position as to throw the common orifice of the Wolffian duct and ureter into the dorsal division, or the ureter alone into the dorsal division and thus produce an anomaly in which the ureter opens into the large bowel. Such conditions have been actually observed.

Gerster has reported a case of a child dying shortly after birth in which autopsy revealed the insertion of the left ureter into a blindly opening rectum. The left kidney and ureter showed dilatation.

Oberteuffer and Revolet have reported a case of an abnormal fetus with both ureters opening into the rectum.

In the year of 1713, Richardson reported an interesting case in which a boy lived "Till he was seventeen years of age and

never made water, and yet was very healthy, vigorous and active. He had constantly diarrhea on him but without much uneasiness. The obstruction must have been in the kidneys for he never had any inclination to make water. He died of a fever."

CLINICAL CASES OF URETERO-INTESTINAL ANASTOMOSIS IN MAN

The first attempt to divert the urinary secretion into the bowel was made by Simon, in 1851. He reasoned that in reptiles and birds the genito-urinary and digestive tracts ended in a common cloaca and that therefore there was no reason why this anatomical arrangement should be incompatible with life in man. This operation was performed on a thirteen-year old boy for exstrophy of the bladder. The patient died twelve months after operation. Both ureters were obstructed by calculi and the ureters and kidneys were seriously diseased. The operations which immediately followed Simon's work are of little or no importance for the subject under consideration in as much as the postoperative term of life was extremely short.

In 1892 Chaput united the right ureter to the rectum in a case of uretero-vaginal fistula. This patient was reported living and her "health very satisfactory" eight years after operation and the ureter on the side of the anastomosis was evidently draining as at that time there were three liquid evacuations in twenty-four hours from the bowel.

Chalot in 1896 did a bilateral uretero-rectal anastomosis in which he removed the ureters for carcinoma of the uterus. This patient was reported living and well one year after operation.

Fowler in 1896 operated upon a boy of six for exstrophy of the bladder. This patient lived to adult life and was then lost sight of.

In a summary in 1901 of the cases which he was able to collect of uretero-intestinal anastomosis by the Madyl operation by Reuben Peterson of Chicago found nineteen cases living and well at the end of one year. Ten cases were living and well at the end of two years; seven cases after three years; four after four years, while one case was living and well at the end of seven years.

Keen in 1875 operated upon a woman thirty-four years of age for vesico-vagino-rectal fistula. He closed completely the vulval opening so that the patient defecated, menstruated and micturated entirely per rectum. This patient was in perfect health twenty-two years after the operation.

Mayo, in an article on "Exstrophy of the bladder," published in December 1917, states that since 1896, thirty-seven patients have been seen with exstrophy of the bladder. Sixteen of these were operated upon with the idea of diverting the urinary stream into the colon. Of these sixteen cases three were operated by the Madyl-Monohan method with two deaths from uremia. The remaining thirteen cases were operated by the transplantation method with one operative death. This leaves twelve cases which survived the operation by the transplantation method. One died from pneumonia three weeks after leaving the clinic; one three years after the operation from pulmonary tuberculosis and another three years after the operation from typhoid fever, thus leaving for study as the remote effects of the absorption of urine ten cases. Nine were operated by the transplantation method and one by the Madyl-Monohan method. Mayo states that the children operated upon were all able to go to school and that the older ones are all working. One young woman has finished a three years course in nursing.

The following case would seem to throw considerable light upon the subject of the remote effects of the prolonged absorption of urine on the body from the intestine in as much as for twenty years urine has been diverted from the left kidney into the bowel and because it is an example of unilateral anastomosis between the ureter and colon. The case is unique and interesting in that this anastomosis was produced by trauma and not made intentionally. It offers points of great interest in that unilateral anastomosis is rarely if ever indicated, one preferring to do a nephrectomy rather than subject a patient to the greater danger of unilateral uretero-intestinal anastomosis.

In bilateral implantations of the ureter into the bowel, the late clinical picture of deterioration of the general health might be ascribed to bilateral infection of the kidney or to gradual

destruction of the kidney by hydronephrosis. So that this case being unilateral with a functioning kidney on the opposite side is of particular interest in that it presents a picture which is in all probability due to the direct effects of absorption of urine.

Mrs. A. G. W. aged forty-seven, married, was first seen for urological examination on August 24, 1917. She complained of very frequent urination, pain at the mouth of the bladder, blindness in the left eye, very marked impairment of vision in the right eye, severe headaches and general weakness. As a child she was not strong and when eight years of age she was taken to a physician because of attacks of pain in the lower abdomen. Menstruation began at the age of eleven, the pain becoming much more intense during the menstrual periods. She usually menstruated for two weeks and at times for as long as three and one half months. When she was eighteen years of age a dilatation and curettage was carried out with the idea that this might relieve the pain accompanying menstruation. She was married at nineteen. Shortly after marriage she was again curetted because of menstrual pain and the year following the operation was again carried out and apparently gave temporary relief. She has never been pregnant. She was again curetted at the age of twenty-seven and examination at this time revealed a mass in the left side. At operation an infected cystlike tumor was found in the left side. This was adherent to the intestines and bladder. A tumor of the right ovary was removed. Following operation she was extremely ill, her temperature at times reaching 106. After two months urine and feces were discharged from the abdominal wound and three weeks later urine was passed per rectum. When urine commenced to be passed by way of the bowel it ceased coming through the abdominal wound but this did not close, fecal matter continuing to be discharged through it. At times gas would be passed per urethram at the end of urination. Seven months after the first operation she was again operated upon and the abdominal wound closed but urine continued to be passed per rectum. Recently following a phthalein test the dye was found in the stool. Since the laparotomy she has had pain in the left upper back in the region of the left kidney.

In May, 1915, she suffered from a severe attack of right lower abdominal pain accompanied by fever and was operated upon for appendicitis. The following year there was a right retinal hemorrhage to be followed recently by another hemorrhage on the same side.

There has been some swelling of the ankles and a hacking cough since December, 1914, but no dyspnea. Severe and prolonged headaches confined chiefly to the occipital region have not been infrequent.

In June, 1916, she suffered from a very severe attack of left renal colic and another attack in August of the same year. During these attacks the urine contained blood and pus. In May of the following year the blood pressure which had been 195 dropped to 120 and the pulse rate increased to 170. Following this the bladder symptoms recurred, urination was frequent and painful and there was hematuria.

Upon examination on June 28, 1915, the cardiac dullness was slightly increased to the left and a rather rough systolic murmur not transmitted to the axilla, was heard at the apex. The systolic blood pressure was 155 and the diastolic 100. The radial vessels were moderately sclerotic and the lower extremities showed considerable pitting. Except for tenderness in the right inguinal region, the abdominal examination was negative.

Urine: twenty-four hour specimen; amount, 1000 cc., specific gravity 1.010; acid reaction, albumin present; no casts seen, a few pus cells.

Phenolsulphonphthalein test: Intramuscular injection of 6 mgm. Total elimination for two hours and ten minutes 65 per cent. (Separate hour determinations were not made.)

Blood nitrogen: 43 mgm. to 100 cc. of blood.

A tabulation of urine notes while under medical care are given below together with the tabulation of blood nitrogen and of blood pressure.

July 16, 1915. Twenty-four-hour specimen amount, 3000 cc.; specific gravity not recorded, but was low.

November 11, 1916. Twenty-four-hour specimen amount 2500 cc.; slightly acid; trace of albumin; occasional hyaline cast.

May 17, 1917. Amount 2400 cc., specific gravity 1.006; strongly alkaline; trace of albumin.

July 12, 1917. Twenty-four-hour specimen; 2400 cc.; feebly alkaline, specific gravity 1.006.

July 26, 1917. Twenty-four specimen; amount 1440 cc.; alkaline, specific gravity 1.006; a great deal of pus.

August 21, 1917. Twenty-four specimen; amount 1600 cc.; specific gravity 1.004; alkaline; albumin present; hyaline and granular casts present; a few pus cells.

Blood nitrogen.

July 10, 1915. There was 33 mgm. to 100 cc. of blood.

July 26, 1915. There was 35 mgm. to 100 cc. of blood.

August 5, 1915. There was 24 mgm. to 100 cc. of blood.

September 29, 1915. There was 22 mgm. to 100 cc. of blood.

November 12, 1915. There was 28 mgm. to 100 cc. of blood.

April 20, 1917. There was 24 mgm. to 100 cc. of blood.

Blood pressure:

July 23, 1915. Blood pressure was 125 systolic and 75 diastolic

August 21, 1915. Blood pressure was 115 systolic and 85 diastolic.

November 29, 1915. Blood pressure was 100 systolic and 70 diastolic.

March 16, 1916. Blood pressure was 135 systolic and 80 diastolic.

July 3, 1916. Blood pressure was 170 systolic and 105 diastolic.

September 11, 1916. Blood pressure was 195 systolic and 120 diastolic.

(At this time headaches were bad and patient was rather dizzy.)

November 13, 1916. Blood pressure was 175 systolic and 110 diastolic.

March 7, 1917. Blood pressure was 175 systolic and 110 diastolic.

May 17, 1917. Blood pressure was 130 systolic and 90 diastolic.

June 14, 1917. Blood pressure was 170 systolic and 110 diastolic.

Functional kidney studies

DATE	N IN- TAKE	N OUT- PUT	NaCl IN- TAKE	NaCl OUT- PUT	WATER IN- TAKE	WATER OUTPUT		DYE	BLOOD NI- TROGEN	SODA TOL- ERANCE
						Day	Night			
	grams	grams	grams	grams	cc.	cc.	cc.	per cent	mgm.	
April 20, 1917.....	13.9	11.5	3	12.4	1800	1600	780	48	24	Normal

Urological examination (Cecil) August 24, 1917

Catheterized specimen of bladder urine: Clear amber color, no albumin, no sugar, few pus cells, no red blood cells, few hyaline casts and a moderate number of deeply staining large bacilli.

Cystoscopic examination: No residual urine. Bladder capacity 60 cc. Cystoscope enters with ease. Trigone shows bulbous edema.

Both ureteral orifices are normal except for some venous engorgement about the right. The bladder shows fine trabeculation and

moderate congestion. At the vertex and a little to the left of the mid-line the bladder seems drawn upward and to the left. No sinuses were seen in the bladder anywhere. Because of the marked pain and irritability of the bladder whether or not the ureters were functioning normally was not determined.

August 27, 1917. Voided specimen of bladder urine: Clear yellow color, no albumin, no sugar. A centrifuged specimen showed a few pus cells, a few hyaline casts and many epithelial cells.

Intramuscular injection of 6 mgm. phenolsulphonphthalein: Urine voided after seventy minutes contained 50 per cent of the dye. Urine voided after second period of sixty minutes contained 13 per cent.

Catheterized specimen of bladder urine: Clear yellow color, no albumin, no sugar. Centrifuged specimen showed a large number of heavy staining bacilli, and occasional pus cell and no casts.

September 5, 1917. Cystoscopy and ureteral catheterization: Both ureteral orifices were well seen. While there was nothing particularly abnormal about the left ureteral orifice and while it definitely showed peristaltic action, no urine was seen to be ejected from this orifice. The right ureter was catheterized easily but upon attempting to introduce a catheter into the left ureter it could be passed for only about two centimeters. The catheter was therefore withdrawn from the left ureter and a small rubber catheter passed into the bladder to collect the urine from the left side transvesically. Specimen of urine collected from the right ureteral catheter: clear yellow color, no albumin. Centrifuged specimen shows an occasional epithelial cell. No red blood cells. No pus cells. No infection. Intravenous injection of 6 mgm. phenolsulphonphthalein: Appeared in the urine from the right ureteral catheter in three minutes. Urine collected from this catheter for fifteen minutes—26 cc.—30 per cent of the dye. Urine collected from this catheter second period of fifteen minutes—17 cc.—17 per cent of the dye. During this period of thirty-three minutes no urine came through the urethral catheter which was put into the bladder to collect the functional study from the left kidney transvesically. The bladder was irrigated gently with a small amount of sterile water which returned and when tested for phenolsulphonphthalein showed none.

September 8, 1917. Cystoscopic examination: Cystoscopic picture of the bladder wall shows the same marked bulbous edema over the trigone as noted in the former cystoscopic study. A better distension was obtained today than at any previous examination and the bladder was studied very carefully for the possibility of any sinus formations

but none was seen. The right ureteral orifice can be seen ejecting urine into the bladder forcibly and rapidly. On the left side the ureter passes through the bladder wall raising it in the formation of a ridge and this ridge undoubtedly shows occasional peristaltic movement but close and prolonged observation of this ureteral orifice fails to show any urine being ejected into the bladder. An attempt to catheterize this ureter was again unsuccessful today. Catheter seemed to pass for about 2 cm. and was then obstructed. On the right side the ureteral catheter was easily passed for about 8 cm. A thorough study of this urine shows it to be free from infection. A urethral catheter was again introduced into the bladder today to repeat the functional study of September 5.

Intravenous injection of 6 mgm. phenolsulphonphthalein appeared on the right side in three minutes. First fifteen minute collection—81 cc.—30 per cent of the dye. No secretion occurred from the bladder catheter during this time.

September 9, 1917. Patient states that after the phenolsulphonphthalein test when her bowels moved the red dye was seen in the bowel movement. It now seemed undoubtedly proven that there was anastomosis between the left ureter and the colon and that the right kidney was free of infection and hypertrophied.

X-ray examination of both kidneys negative.

Left nephrectomy (Cecil) was done on September 13, 1917. After opening the renal fossa a long kidney could be felt. The fat was extremely adherent to it. The kidney was difficult to draw down on account of adhesions at the upper pole. On palpation it was irregular and there were areas of softening and induration. The pelvis was moderately dilated and the ureter measured 1 cm. in diameter. This ureter was followed down to the brim of the pelvis so that no anastomosis with the bowel occurred to this point. Patient reacted splendidly following the operation. Urine was voided within four hours. Patient was discharged from the hospital on the twenty-fourth day although the wound had healed on the tenth day.

Note: September 10, 1918. Patient seen today almost one year after operation. Her health has steadily improved. She now takes long walks. Appetite and digestion are good. Suffers very slightly with headaches. Is immensely better than when seen one year ago.

The work of Baird, Scott and Spencer has shown rather conclusively that the entire urinary output cannot be diverted into

the upper intestinal tract without producing fatal results. Mayo found that in doing ureteral implantations that it was preferable to implant first one ureter and subsequently the other because mental apathy came on after the diversion of the urinary stream into the lower bowel. He states that this condition soon passes off.

The marked toxic symptoms in the case which we have reported would seem to us in a large measure to be dependent upon absorption of urine from the colon although the great improvement following the left nephrectomy might have been somewhat dependent upon the removal of an infected kidney. It has not been our experience however to find such extreme toxic symptoms associated with unilateral pyelonephritis.

In conclusion the work of Coffey and Mayo has demonstrated that the ureter can be implanted into the bowel from a technical standpoint and that the diversion of the urinary stream into the lower bowel is not incompatible with rather long terms of life. It would seem, however, that urinary products can be absorbed even though the implantation be made low down in the large bowel and that the prolonged absorption of these products may eventually produce a picture not unlike chronic nephritis.

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CONCERNING THE ABSORPTION OF DRUGS AND POISONS FROM THE URETER AND PELVIS OF THE KIDNEY

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In the two preceding communications in this journal (1, 2), the author has discussed the question of absorption of drugs from the bladder and urethra and described his experiments on the subject. It was shown that the bladder and urethra differ markedly in their absorptive power for drugs and poisons. Following the above observations, it was but natural to inquire into the possibility of absorption of various pharmacological agents from other parts of the urinary tract. Accordingly experiments were undertaken to determine the possibility of absorption and the degree of the same for various substances from the ureter and the pelvis of the kidney. In the present paper the results of these experiments are briefly described.

METHOD

Absorption of drugs from the ureter was studied in dogs. In order to exclude the possibility of error through absorption through other channels such as the peritoneum and the bladder, the following procedure was followed:

An incision was made just below the floating ribs and the kidney exposed. A glass cannula was then inserted into the ureter just below the kidney pelvis pointing distalward. A fine ureteral catheter was passed through the ureter from above downward and its insertion in the bladder located. An incision was then made in the abdominal wall just above the bladder and another cannula, with a small rubber tube attached, was inserted into the lower end of the ureter pointing upward. Par-

ticular pains were taken to ligate the cannulae tightly so as to prevent leakage of the perfusing fluid. The whole length of the ureter was thus perfused with a saline solution by injecting the fluid under low pressure into the upper cannula and allowing the solution to escape from the lower cannula and rubber tubing without coming in contact with the peritoneum or entering the bladder. In this way normal physiological saline solutions and saline solution containing the drug to be studied could be per-

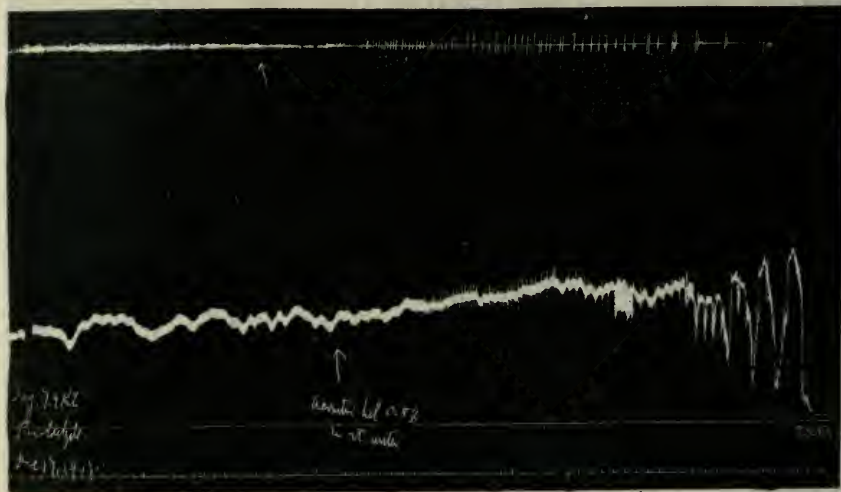


FIG. 1. ABSORPTION OF ACONITIN HYDROCHLORIDE FROM URETER OF A DOG

Paraldehyde anesthesia. Ureter perfused from above downwards, without the solution coming in contact with the peritoneum or the bladder. Upper curve = respiratory tracing. Lower curve = blood pressure tracing.

fused through the ureter alone and the absorption of drugs or poisons studied at ease.

In order to study absorption of drugs from the kidney pelvis the procedure in the first steps was the same as above. An incision being made below the floating ribs, the kidney was exposed and its pelvis freed from surrounding structures. A good sized glass cannula was then inserted into the pelvis and ligated pointing upward or toward the kidney. A fine ureteral catheter was then inserted inside of the glass cannula and the perfusing

fluid injected through the fine catheter. A drug in solution could thus be brought in contact with the pelvis of the kidney under low pressure and the fluid allowed to run back around the catheter through the glass cannula without coming in contact with the peritoneum or surrounding tissues.

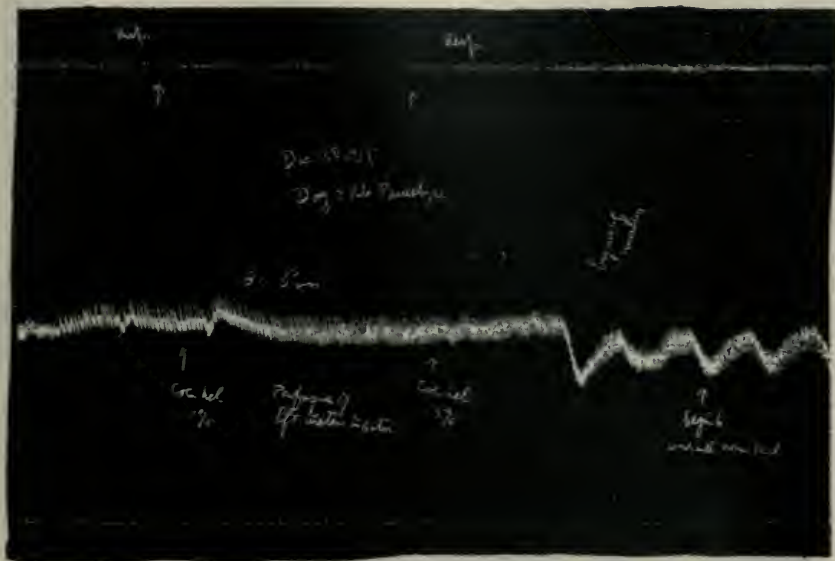


FIG. 2. ABSORPTION OF COCAIN HYDROCHLORIDE FROM URETER OF A DOG
Upper curve = respiratory tracing. Lower curve = blood pressure tracing.

RESULTS

In order to determine whether drugs could be absorbed from the organs in question a few typical bodies were experimented with, the ease of the absorption of which from other organs such as the urethra, the vagina, etc., had already been studied. The following substances were used: apomorphin, aconitin, cocaine, and potassium cyanid.

The effect of the absorption of apomorphin could be studied by noting retching and vomiting movements produced by its action on the vomiting centre. It was actually found that the perfusion of the ureter and of the kidney pelvis with a solution

of apomorphin 1 per cent under very little pressure did produce vomiting movements in an anaesthetized animal thus indicating the absorption of the alkaloid through the walls of those organs.

The absorption of potassium cyanid solution 1 per cent through the walls of the ureter and kidney pelvis could, in the same way, be demonstrated by the study of the respiratory and blood pressure curves.

Absorption of cocain hydrochloride through the ureter and the pelvis of the kidney was established by observing, on the one

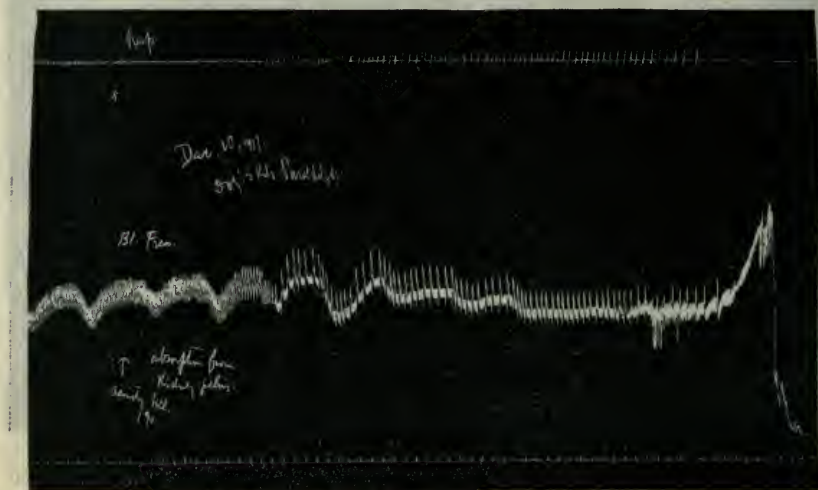


FIG. 3. ABSORPTION OF ACONITIN HYDROCHLORIDE FROM PELVIS OF KIDNEY IN A DOG

Note effect on respiration and blood pressure

hand, the effect of cocain after absorption on the respiration and the blood pressure and, on the other hand, its convulsive action on the central nervous system. This is illustrated by the figure 2.

Finally, absorption of the powerful alkaloid aconitin-hydrochloride was very easily and strikingly shown by its effect on the respiration and especially on the heart and blood pressure. The accompanying figures illustrate some of the experiments which were performed.

SUMMARY

It is thus seen by the study of aconitin, cocain, apomorphin and potassium cyanid that these drugs or poisons are easily absorbed through the walls of the ureter and the kidney pelvis. Further experiments with other drugs, in view of these striking results, were deemed unnecessary. The above findings, it may be added, are not only of theoretical scientific interest but are also of some practical importance and should be borne in mind by the practical urologist inasmuch as various drugs such as silver compounds, thorium, etc. are introduced into these organs for diagnostic and therapeutic purposes.

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BOOK REVIEW

Modern Urology. Edited by HUGH CABOT, M.D., Chief of Genito-Urinary Department of the Massachusetts General Hospital. Assistant Professor of Genito-Urinary Surgery in the Harvard Medical School, Boston, Mass.

The work consists of a series of monographs by twenty-nine of America's leading urologists. The field of urology is adequately covered and each subject is exhaustively handled. A pleasing feature of the work is the space devoted to the consideration of the gross and microscopic pathology of the disease in question. Almost without exception this phase of the subject is taken up in detail, a noteworthy omission in many less pretentious works. The subject matter throughout is attractively presented and the text is profusely illustrated. It is unquestionably the most comprehensive and authoritative of modern texts which have appeared in English.

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